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PAIN AND POSTOPERATIVE HEMORRHAGE AFTER TONSILLECTOMY

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ACADEMIC DISSERTATION

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To my family

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Helsinki, September 2019
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ABSTRACT

Studies have shown that acute postoperative pain is still undertreated in many common surgical procedures such as tonsillectomy, as pain may go unnoticed in everyday practice. Recovery after tonsillectomy may be complicated also by post-tonsillectomy hemorrhage (PTH), which can even be life threatening. The aim of this study was to investigate immediate complications after tonsillectomy particularly pain and PTH, and to evaluate the evidence regarding the analgesic effect of systemic analgesics and dexamethasone for post-tonsillectomy pain and whether topical ropivacaine is effective in the prevention of pain. Studies I and II are retrospective chart reviews including 1533 outpatients operated for tonsillectomy over one year in our institution, that analyzed the incidence of PTH in adult patients (Study I) and the incidence of all postoperative complications of pediatric patients (Study II), and their association with perioperatively administered medications. Study III is a systematic review and meta-analysis on analgesics and dexamethasone for the prevention or treatment of post-tonsillectomy pain in adults and adolescents including 29 randomized, double-blind, placebo-controlled studies. Study IV is a prospective double-blind placebo-controlled study on topical ropivacaine applied to tonsillar beds after removal of tonsils for the prevention of post-tonsillectomy pain in 154 adult patients.

In retrospective studies, PTH was the most common complication. Incidence of PTH in adults was 14.5%, and in pediatric patients 7.1%. In pediatric patients the overall incidence of unplanned postoperative contacts was 14%, (revisits 10%, re-admission 8%, pain 3%, fever 2.3%, PONV 1%). Paracetamol, nonsteroidal anti-inflammatory agents, dexamethasone or oxycodone were not associated with an increased risk of postoperative complications in adult or in pediatric population. Among pediatric patients, the use of local peritonsillar infiltration of lidocaine with epinephrine was associated with an increased risk of secondary PTH. In the systematic review, the main finding was the scarcity of data and short duration of follow-up in the included studies. Paracetamol, NSAIDs, dexamethasone, gabapentinoids and dextromethorphan had weak to moderate analgesic efficacy on the day of operation, dexamethasone in multiple doses beyond one day. The mean intensity of pain was moderate to severe for 1-2 weeks despite of medication among adult patients in Studies III and IV. In prospective Study IV, topical ropivacaine failed to reduce post-tonsillectomy pain during the first postoperative week but reduced the need for paracetamol-codeine during the second postoperative week (secondary outcome).

In conclusion, PTH is a common complication, especially in adults. The use of peritonsillar infiltration of lidocaine with epinephrine was associated with increased risk of secondary PTH among pediatric patients. Systematic review revealed that the evidence on efficacy of analgesics for post-tonsillectomy pain is still minimal due to lack of good quality studies with long enough follow-up. Pain intensity is usually moderate to severe for more than one postoperative week. Single analgesics are not effective enough to provide clinically meaningful reduction of pain intensity, and thus multimodal pain management is needed. Topical ropivacaine failed to reduce post-tonsillectomy pain during the first postoperative week but seemed to modify pain during the second postoperative week.

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which will be referred to in the text by their Roman numerals:

- I Tolska HK, Takala A, Pitkaniemi J, Jero J. Post-tonsillectomy haemorrhage more common than previously described—an institutional chart review. *Acta Otolaryngol* 2013;133:181-6.
- II Tolska HK, Takala AJ, Jero J. Peritonsillar infiltration of lidocaine with adrenaline is associated with increased risk of secondary post-tonsillectomy haemorrhage. *J Laryngol Otol* 2018;132:911-922.
- III Tolska HK, Takala A, Hamunen K, Kontinen V. Systematic review on analgesics and dexamethasone for post-tonsillectomy pain in adults. *Br J Anaesth*. 2019;2:e397-e411.
- IV Tolska HK, Takala A, Blomgren K, Hamunen K, Kontinen V. Topical ropivacaine in prevention of post-tonsillectomy pain in adults. *Anesth Analg* 2017;124:1459-1466.

ABBREVIATIONS

AHI	Apnea/hypopnea index is used for classification of severity of sleep apnea. It is represented by the number of apnea and hypopnea events per hour of sleep which must last for at least 10 seconds and be associated with a decrease in blood oxygenation.
APS-OPC	Acute Pain Service Outpatient Clinic
ASA	American Society of Anesthesiologists
BPI	Brief Pain Inventory
CI	Confidence interval
COX	Cyclooxygenase (enzyme)
EMA	European Medicines Agency
ESPA	European Society for Paediatric Anaesthesiology
IQR	interquartile range
i.v.	Intravenous (route of administration)
Na+	Sodium
NMDA	N-methyl-D-aspartate
NNT	Number needed to treat
Nociceptor	Pain receptor, sensory neuron that responds to damaging or potentially damaging stimuli by sending “possible threat” signals to the spinal cord and the brain
NRS	Numeric rating scale
NRSr	Numeric rating scale at rest
NRSs	Numeric rating scale on swallowing
NSAID	Nonsteroidal anti-inflammatory drug
OIH	Opioid-induced hyperalgesia
OR	Odds ratio
OSA	Obstructive sleep apnea
oSDB	Obstructive sleep-disordered breathing
Outpatient surgery	Surgery that does not require an overnight hospital stay; same as day surgery
PACU	Post-anesthesia care unit
p.o.	Peroral (route of administration)
Pod	Postoperative day
PONV	Postoperative nausea and vomiting
PTH	Post-tonsillectomy hemorrhage
PTH, primary	Post-tonsillectomy hemorrhage within 24 hours of operation
PTH, secondary	Post-tonsillectomy hemorrhage after 24 hours after operation

Abbreviations

RCT	Randomized controlled trial
RR	Risk ratio
SD	Standard deviation
VAS	Visual analog scale
VRS	Visual rating scale

1. INTRODUCTION

Tonsillectomy is the most common otolaryngological procedure globally and is usually performed as an outpatient surgery.^{1,2} In Finland, approximately 7900 procedures, and in the United States more than 500 000 procedures, are performed annually.¹⁻⁵ Recovery may be complicated by post-tonsillectomy hemorrhage (PTH), intense pain, postoperative nausea and vomiting (PONV), and dehydration.⁶⁻⁷ PTH can even be life threatening.

Although tonsillectomy is a common operation, consensus on optimal pain management strategy is still missing. NSAIDs and dexamethasone are used in the prevention and treatment of post-tonsillectomy pain and reduction of opioid requirements and PONV, however association with an increased risk of PTH has been suspected.⁸⁻¹⁸ In adults, the indication for tonsillectomy is most commonly recurrent or chronic tonsillitis, whereas in pediatric patients it is hypertrophy. Chronic tonsillitis requires more dissection and coagulation, which leads to more intense pain, and therefore weak opioids are usually needed. For pediatric patients, use of opioids has been recently restricted due to reports of serious respiratory depression.¹⁹⁻²⁴ Fortunately, tonsillotomy in which only part of tonsils are removed, has become more common technique and as it is less painful, opioids are not necessarily needed.⁴ Local anesthetics are used commonly in different types of surgeries as part of multimodal analgesia.²⁵ For post-tonsillectomy pain, modest efficacy of local anesthetics has been found in pediatric populations, but in adults only small heterogeneous studies with less than optimal quality exist.^{26,27}

The incidence of unplanned postoperative contacts to hospital is often used as an estimate of quality of perioperative treatment.^{7,28} In our institution in a prospective study (2003) in pediatric patients, the incidence of unplanned return visits was 13% (PTH 8%, unable to eat 2%).²⁸

In the present thesis, the main purpose was to study how patients recover from tonsillectomy with emphasis on the most common postoperative complications—PTH and pain. The incidence of complications in our institution (PTH in adults and all immediate complications in pediatric patients), and whether perioperative medication influences them was investigated in a large retrospective study. The efficacy of perioperative analgesics and dexamethasone for post-tonsillectomy pain was studied in a systematic review and meta-analysis. Local anesthesia with topical ropivacaine for the prevention of post-tonsillectomy pain in adults was examined in a prospective study.

2. REVIEW OF LITERATURE

Tonsillectomy was first described in Western literature by Celsus in 50 A.D. and in Hindi medicine 3000 years ago, being probably one of the oldest surgical procedures.²⁹

The tonsils are lymphatic tissue and are part of the body's immune system, the part in which immune responses against antigens entering the body through the mouth or nose are initiated. The greatest immunologic activity of the tonsils is found between the ages of 3 and 10 years. The epithelium of the tonsils is cryptic and contains a system of specialized channels lined by "M" cells, which take up antigens into vesicles and transport them to the lymphoid follicles, where dendritic cells and macrophages process the antigens and present them to helper T lymphocytes which then stimulate proliferation of follicular B lymphocytes and their development into either antibody-expressing B memory cells or plasma cells that produce antibodies.³⁰ In chronic tonsillitis, the controlled process of antigen transport and presentation is altered due to shedding of the M cells from the tonsil epithelium.³⁰ The tonsillar lymphocytes can become so overwhelmed with antigenic stimulation that they may be unable to respond to other antigens. Once this immunologic impairment occurs, the tonsil is no longer able to function adequately in local protection or to reinforce the secretory immune system of the upper respiratory tract.³⁰ The therapeutic advantage of removing recurrently or chronically infected tonsils causing symptoms such as pain in throat and fever, is based on this pathology.

The main indications for tonsillectomy are as mentioned chronic tonsillitis, recurrent peritonsillar abscess, and tonsillar hypertrophy causing obstructive sleep-disordered breathing (oSDB) or sleep apnea, periodic fever (pediatric patients), and suspicion or treatment of malignancy.³¹ oSDB is a clinical diagnosis "characterized by obstructive abnormalities of the respiratory pattern or the adequacy of oxygenation or ventilation during sleep (snoring, mouth breathing, and pauses in breathing)."³² oSDB includes a spectrum of obstructive disorders that increase in severity from primary snoring to obstructive sleep apnea (OSA). Studies have shown that disease-specific and global quality of life improve after tonsillectomy has been performed for recurrent or chronic sore throat, or oSDB.³²

Tonsillectomy is defined as a surgical procedure performed with or without adenoidectomy that completely removes the tonsil, including its capsule, by dissecting the peritonsillar space between the tonsil capsule and the muscular wall (Figure 1).³² In our institution (Helsinki University Hospital, Department of Otorhinolaryngology—Head and Neck Surgery), the main technique is cold dissection in which tonsils are removed with cold steel instruments and hemostasis

is achieved by coagulating bleeding vessels with bipolar forceps as necessary. The area is left open to heal, and sutures are not needed. Other techniques include hot techniques (bipolar diathermy scissors, ultrasound scissors, coblation) and variations of these. Tonsillectomy is usually performed under general anesthesia with endotracheal intubation. For pediatric patients a (reinforced) laryngeal mask instead of endotracheal tube is also being used.³³ In tonsillotomy, tonsillar tissue causing obstructive symptoms is removed partially without touching the surrounding tissue (performed mainly for pediatric patients).

Tonsillectomy is usually performed as outpatient surgery, and patients are discharged on the day of operation, a practice that has proven to be safe with appropriate patient selection.³⁴ In many institutions, including ours, patients are discharged 6 hours after surgery. Most of primary PTHs occur within 6 hours after surgery, and PTH between 8–24 hours is extremely unlikely.³⁵ Therefore, monitoring for primary hemorrhage using overnight admission is not useful. Patients prefer recovering at home, and in addition risk of infections and costs are reduced.

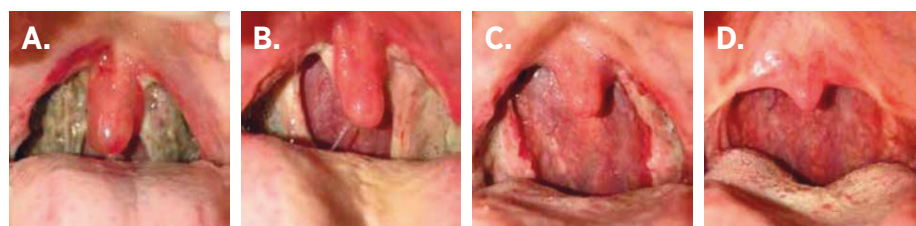


Figure 1. Tonsillectomy. A. On the day of operation. B. Sixth postoperative day; fibrin clot starts to detach, and the risk of post-tonsillectomy hemorrhage is at its highest. C. Two weeks after tonsillectomy healing is not yet complete. D. Four months after surgery the mucosa of the tonsillar beds has healed. Reproduced with permission from Mäkinen LK, Nokso-Koivisto J. Tonsillectomy. *Duodecim* 2019;135:69-75.

2.1. COMPLICATIONS AFTER TONSILLECTOMY

2.1.1. INCIDENCE OF COMPLICATIONS

In large register studies, the incidence of unplanned postoperative return visits is around 6–8% among pediatric patients (PTH 2–3%, dehydration 2–3%, pain 1–2%, readmissions 0.5–1%); in adult patients two times higher (except for dehydration, which is more common among pediatric patients).^{36,37} In prospective studies the incidence of complications seems to be even higher, most probably due to more accurate data gathering.⁷ In a prospective study in Denmark in 2012 including 614 tonsillectomy outpatients, the incidence of unplanned postoperative contact was 23% (pain 12%, PTH 4%, PONV 2%, readmissions 5%), and the indication of chronic tonsillitis and higher age increased the risk of unplanned contact (31%

of adults vs. 18% of children).⁷ In our institution in a prospective study (2003) including 100 pediatric patients, the incidence of unplanned return visits was 13% (PTH 8%, unable to eat 2%).²⁸

Other complications include fever (usually 18–36 hours after surgery), respiratory problems (laryngospasm, obstructive symptoms, pulmonary edema as a result of sudden relief of the excess positive end-expiratory pressure after the tonsils are removed), operative trauma to the surrounding tissues, nerve lesions of the nervus lingualis (taste disorder, neuralgia) and glossopharyngeal nerve (velopharyngeal insufficiency with nasal regurgitation, secondary neuralgia, otalgia), and dislocation of cervical vertebra (patients with Down syndrome have atlantoaxial joint laxity and are at risk of subluxation during manipulation of the neck and suspension with a mouth gag).³⁸ Although tonsils are lymphatic tissue and part of the body's immune system, and minor alterations in immunoglobulin concentrations in serum have been demonstrated in some studies, their removal has not been associated with increased incidence of upper respiratory tract infections.^{30,40} However, an increased risk of rare deep neck infections has been reported (1.7 times greater in tonsillectomized patients).⁴¹

Reported rates of outpatient tonsillectomy mortality varies between 1 in 18 000 to 1 in 56 000 internationally.³¹ About one-third are related to PTH, the rest to aspiration, cardiopulmonary failure, electrolyte imbalance, or anesthetic complications.³¹ Airway compromise is the major cause of injury and death in malpractice claims.³⁷ In Finland, 4 patients (age 15–34 years) have died between 2007–2017 due to secondary PTH; in two cases 3 days postoperatively, in two cases 10–11 days postoperatively (unpublished data, Archive of death certificates, Statistics Finland).

2.1.2. POST-TONSILLECTOMY HEMORRHAGE

PTH occurs in a two-peak mode: primary PTH (within 24 hours of operation) and secondary PTH (24 hours after operation), usually at around postoperative days 4 to 7, secondary PTH being more common.⁴² The pattern of PTH and pain can be understood by pathology of tonsillectomy and by the physiological healing process. Surgical and thermal damage to the mucosa, muscles, and nerve endings cause inflammation, swelling, and pain as pharyngeal nociceptors are stimulated.⁴² Pain usually reaches its maximum at postoperative days 3–7 (depending on the extent of surgery), which corresponds to the maximal wound inflammation documented in experimental models. As the coagulation cascade activates, a fibrin clot is formed on top of the scar, under which renewing epithelium starts to grow. The fibrin clot detaches on around the seventh postoperative day, leaving the regenerative capillaries open to irritation, and during this time secondary PTH is most common.

When epithelialization is completed at the end of the second postoperative week, PTH rarely occurs and pain diminishes significantly.⁴²

The incidence of PTH in the literature varies from 0 to 40% due to the inconsistent criteria of bleeding and type of data gathering. If data are analyzed more systemically, the range narrows down.⁴³ Results depend on whether data collected are from patient questionnaires including all minor bleeding episodes that stop spontaneously (in prospective studies), patient charts including all contact with the hospital due to bleeding (in retrospective studies), or register studies including only revisits and reoperations, making it difficult to compare results.

For systematic improvement of care and benchmarking, national quality registers are nevertheless essential. National quality registers are the most developed in Sweden, including over 100 medical quality registers, of which nine focus on ear, nose, and throat diseases.⁴⁴ At the moment, an international tonsil surgery quality register is being established for Denmark, Finland, Norway, and Sweden by the Nordic Tonsil Surgery Register Collaboration.⁴⁵

A higher risk of PTH is associated with indication for surgery (secondary hemorrhage more common with chronic tonsillitis and previous peritonsillar abscess than with tonsillar hypertrophy), male gender, and older age.^{46,47} In adults, indication is mainly recurrent infection requiring more dissection, and therefore risk of PTH and pain intensity may increase, compared with pediatric patients operated mainly for tonsillar hypertrophy. Hot techniques (bipolar diathermy scissors, ultrasound scissors, coblation), which affect a deeper and larger area around the tonsils, are associated with a higher risk of secondary PTH and an increased pain intensity compared with cold steel dissection.⁴⁸ Tonsillotomy has lower risk of PTH than tonsillectomy, and therefore tonsillotomy has become the preferred type of tonsil surgery for pediatric patients in recent years.³⁶ In tonsillotomy, tonsillar tissue causing obstructive symptoms is removed partially without touching the surrounding tissue, resulting in less pain, a reduced number of days of analgesic use, fewer days to return to a normal diet, less dehydration, and a lower rate of PTH and readmissions.⁴⁹⁻⁵⁰

2.1.3. POST-TONSILLECTOMY PAIN

Studies have shown that managing postoperative pain is still a challenge, and in some operations that have high pain intensities patients do not receive enough analgesia.^{51,52} Although good analgesic techniques exist, they are not used, possibly because pain goes underestimated in everyday practice. A prospective cohort study of 116 000 patients collected data on pain intensity on the first day after 179 surgical procedures in Germany in 2013.⁵² It found that patients reported high pain scores after many “minor” surgical procedures, including tonsillectomy, appendectomy,

cholecystectomy, and hemorrhoidectomy, which ranked among the 25 procedures with highest pain intensities. These patients typically received no or low doses of opioids which, according to the authors, indicated that high pain intensities were often ignored or not taken seriously, so that analgesic administration was delayed and/or insufficient.

Post-tonsillectomy pain has been known to be intense, lasting for several days; however, in most studies follow-up periods cover only the early postoperative days.⁵³ Postoperative pain types were analyzed in a questionnaire-based study on 335 patients in 2012 in Austria.⁵⁴ Five pain types were identified (Figure 2). Pain type I (25%), characterized by a constant low level of pain was more common in pediatric patients (≤ 15 years) compared with adults ($p < 0.001$). Severe and/or increasing pain types III, IV, and V were more common in adults ($p < 0.034$). In pain types IV and V, pain is severe for 2 weeks. The most frequent pain type, type II (50%), with severe pain until the sixth to seventh postoperative day, then declining, was similarly distributed between both age groups ($p = 0.21$). Patients with increasing pain (types III and IV) and pain type V showed significantly higher risk for PTH.

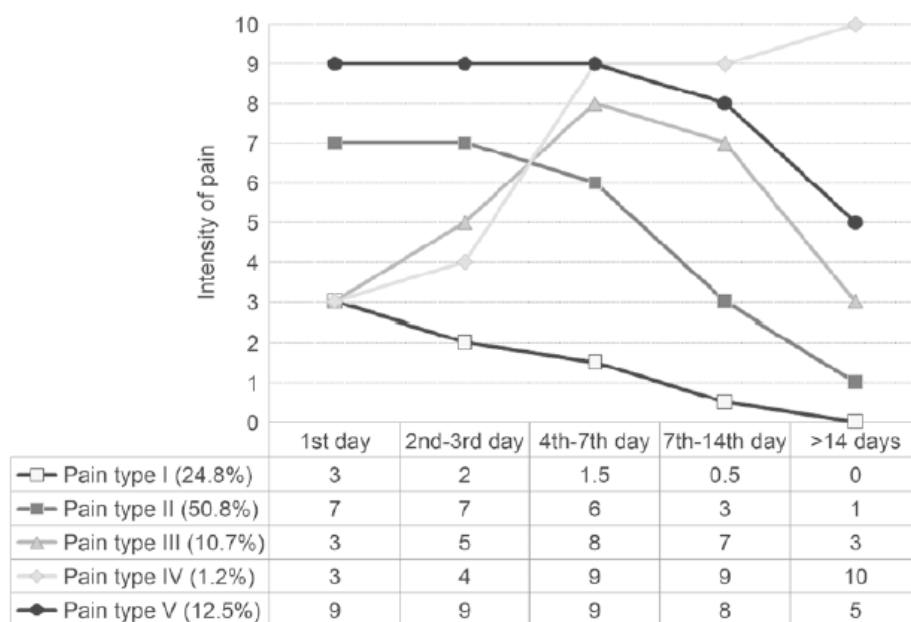


Figure 2. Incidence of pain types (percentage; %). Pain intensity reported as mean value during each period. Reproduced with permission from Sarny S, Habermann W, Ossimitz G, Stammberger H. Significant post-tonsillectomy pain is associated with increased risk of hemorrhage. *Ann Otol Rhinol Laryngol.* 2012;121:776-81.⁵⁴

2.2. PAIN PATHWAYS AND PROCESSING

The pain stimulus caused by tissue damage leads to a series of electrical and chemical events that ultimately result in sensing and experiencing pain. Physiological events that lead to pain sensation in the nervous system can be divided into four stages (Figure 3). Initially, a pain stimulus is produced in the tissue when the nociceptors (nerve endings in the primary afferent neurons) or as recently discovered, pain-receptive Schwann cells, are activated through mechanical, chemical (inflammatory mediators), or thermal stimulation of the tissue that causes electrochemical activation of nerve endings, leading to the generation of action potentials in the nerve cell (transduction). The pain signal is then transmitted through the nerve cells to the parts of the central nervous system (transmission) where the pain is sensed (perception). Pain is altered in the nervous system by inhibitory descending pathways (modulation).⁵⁵

After injury, continuous release of inflammatory mediators sensitizes nociceptors marked by a decreased threshold for activation (peripheral sensitization), clinically observed in the tissue injury area as primary hyperalgesia (pain is perceived as more painful than it would otherwise have been) and pain response from stimuli which do not normally provoke pain (allodynia), which are normal protective responses, that subside as tissue is healed. Strong and long-lasting noxious input from the periphery may result in central sensitization (persistent postinjury changes in the central nervous system that result in pain hypersensitivity) and hyperexcitability (exaggerated and prolonged responsiveness of neurons to normal afferent input after tissue damage).⁵⁶ Clinically, the unaffected normal area around the tissue injury becomes sensitized to pain (secondary hyperalgesia), its extent correlating with the risk of chronic postsurgical pain / persistent postoperative pain. The subacute phase (4–6 weeks postoperatively) seems to be critical in that if pain continues, or gets worse, the underlying central sensitization process is maintained, and long-lasting neuroplastic changes in the dorsal horn of the spinal cord may occur (“pain memory”), which may cause acute pain to become chronic.^{57,58}

The neural circuits in the dorsal horn are complex, and various neurotransmitters, second messengers (e.g., substance P, protein kinase C), and receptors (e.g., N-methyl-D-aspartate [NMDA]) are involved in the process of nociception and in acute and chronic pain.⁵⁹

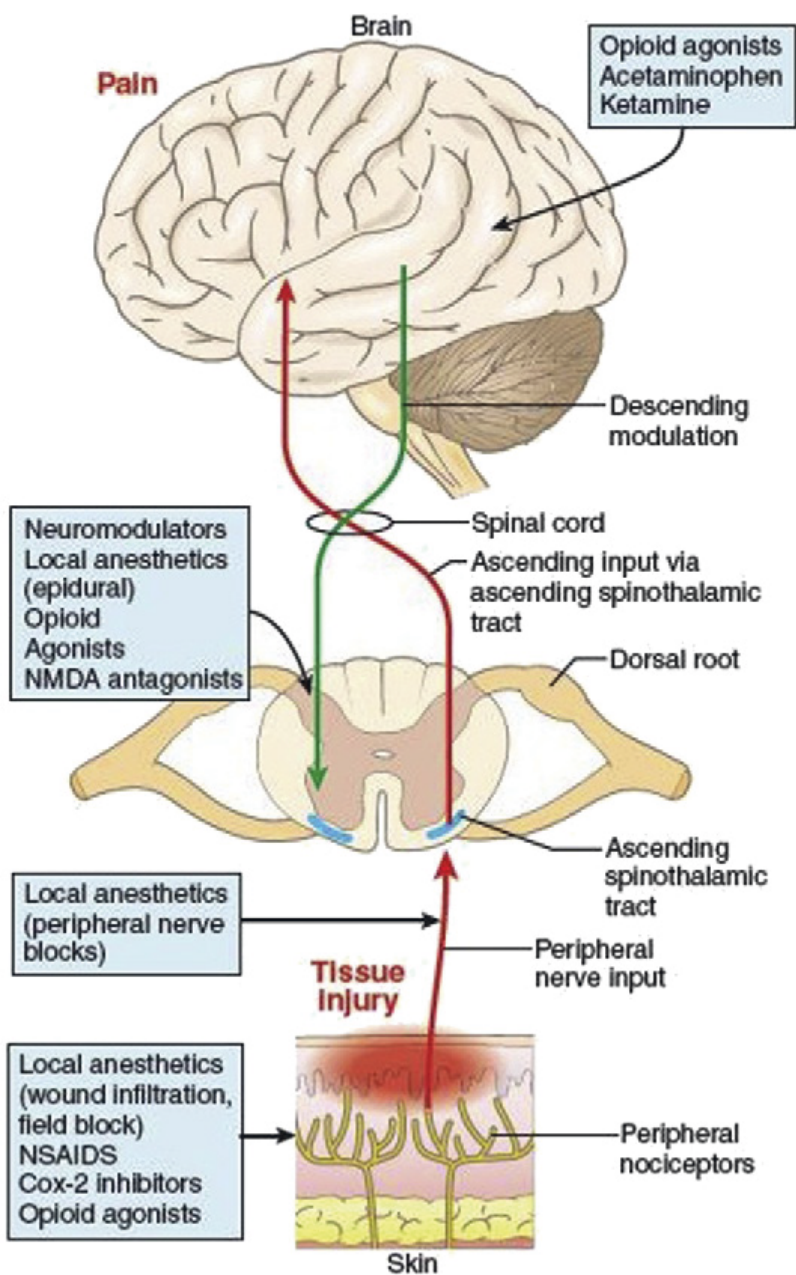


Figure 3. The pain pathway in the central and peripheral nervous systems and the sites of action for each class of medication. COX-2, cyclooxygenase-2; NMDA, N-methyl D-aspartate; NSAIDs, nonsteroidal anti-inflammatory drugs. Reproduced with permission from Kohring JM, and Orgain NG. "Multimodal Analgesia in Foot and Ankle Surgery." *The Orthopedic Clinics of North America* 2017;4:495-505.

2.3. PAIN MEASUREMENT

Pain is a personal experience. The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”. Measuring pain and its changes are needed in evaluating treatment responses in clinic practice and in research. The Numerical Rating Scale (NRS), Visual Analogue Scale (VAS), Verbal Rating Scale (VRS), and Faces Pain Scale-Revised (FPS-R) are validated measures of pain intensity.⁶⁰ The most commonly used is VAS (visual analogue scale), a continuous scale comprised of a horizontal line, usually 10 centimeters (cm) in length. Patient marks a vertical line at the intersection, which he/she estimates to reflect the intensity of pain. Left end of VAS line corresponds to a situation where the patient has no pain at all, while the right end corresponds to the worst possible pain. In NRS (numeric rating scale), numbers (usually from 0-10) describe pain intensity in which 0 stands for no pain, 1 to 3 mild pain, 4 to 6 moderate pain, and 7-10 severe/strong pain. In VRS (verbal rating scale) words describe intensity of pain (4 to 6 points) which can be converted to numbers. Children of 3-4 years of age can use simple verbal scales and graphical pain facial scales such as FRS-R or Wong-Baker faces scale, and at the age of five or more VAS and its’ modifications. In young and severely ill children, pain and its changes are assessed by observer (changes in behavior, posture, facial expressions, sound, skin color, heart rate, and response to treatment). When measuring pain, both pain at rest and during movement (dynamic pain) should be assessed.⁶¹ Consumption of analgesics and need for rescue medication are also used as end-points/outcomes in research.

Currently, more comprehensive patient reported outcomes (PROs) of the recovery experience (pain, sleep, function, mood), that reflect the impact of a disease/condition to daily life, are recommended to be used. Brief pain inventory (BPI) is a validated tool that documents both the intensity of pain (sensory dimension) and interference of pain in the patient’s life (reactive dimension). It was originally developed by World Health Organization (WHO) for cancer patients and has been found reliable and valid in different pain states across cultures and languages.⁶²

2.4. PAIN MANAGEMENT PRINCIPLES

Patient-centered care is a foundation and source of effective, safe and valuable treatments. It is achieved by building a partnership between clinician and patient. Clinician shares information and discusses treatment options gathering information on patient’s own expectations and goals - open dialogue in which patient is involved in treatment considerations, called shared decision making.

For acute postoperative pain, multimodal (opioid-sparing) analgesia has become the standard of care. According to the International Association for the Study of Pain (IASP), it is defined as “the concurrent use of separate therapeutic interventions with different mechanisms of action within one discipline aimed at different pain mechanisms” with the rationale to target simultaneously multiple places in the nociceptive system at smaller doses to maximize the analgesic effect while minimizing adverse events.⁶² Multimodal analgesia is an integral part of enhanced recovery after surgery (ERAS) concept, which is a perioperative care pathway designed to achieve early recovery for patients undergoing major surgery (erassociety.org).

Minimizing need for opioids is essential for optimizing recovery of patients after surgery. Although opioids are the most effective analgesics, they have many adverse effects. High doses of intraoperative opioids may produce counter effects because of neuroadaptation; enhancement of existent pain and facilitation of chronic pain development.⁶¹ Opioid tolerance (pharmacological concept) and opioid-induced hyperalgesia (OIH, a clinical syndrome) develop, opioid requirements increase postoperatively, and recovery does not proceed optimally. Opioid-sparing therapeutic interventions that are combined include regional anesthesia, non-opioid analgesics, and adjuvants that optimally have additive or synergistic effects producing superior analgesia while decreasing opioid-related side effects. Several adjuvant drugs commonly used in perioperative anesthesia attenuate the development of OIH: ketamine, gabapentinoids, magnesium, dexmedetomidine, lidocaine, and nitrous oxide, also called “antihyperalgesic adjuvants.”⁶³ They are increasingly studied for their efficacy to provide opioid-less and opioid-free anesthesia.

Liberal prescription and illegal use of opioids have led to an opioid crisis in the United States, and opioid exposure has become the leading cause of death related to unintentional injury.⁶⁴ In previous years, the potential of weak opioids (prescribed for postoperative or chronic pain) to cause addiction has been underestimated. However, recent studies show that 1–10% of opioid naive patients that have received prescription of opioids for postoperative pain become chronic users.^{65,66} In the study by Brat in 2018, duration rather than dosage correlated with misuse; each week and every renewed prescription were associated with an increase in misuse of 44%.⁶⁴ Identified risk factors for addiction include age (> 55 years of age, and also young age), female gender, low income, smoking and alcohol use, certain surgical procedures, and depression.⁶⁷

If a patient needs opioids for postoperative pain at home, follow-up is essential to ensure that opioids are not continued beyond the normal healing process and addiction does not develop or is treated in time. One of the goals of the Acute Pain Service Outpatient Clinics (APS-OPCs) is to ensure that strong opioids are not inappropriately continued after recovery. The goal is to provide continuing active pain management after discharge from hospital by effective multimodal

analgesia so that opioids may be attenuated and in order to prevent chronic pain. A patient is referred from a surgical unit to an APS-OPC in a situation where he/she has severe pain, needs strong opioids and/or large doses of neuropathic pain medication at discharge after surgery, there is problematic postoperative pain at home, or in case of prolonged need for pain medication. The first APS-OPC in the world was started in 2012 in Helsinki University Hospital, Finland, and a 2-year follow-up study showed that a significant number of surgical patients benefited. At discharge after surgery, 54% of patients were using weak opioids, 32% strong opioids, and 71% gabapentinoids; at discharge from the APS-OPC, the numbers were 20%, 6%, and 43% respectively, and 22% of the patients had been referred to the multidisciplinary pain management services for further pain management.⁶⁸ The median time from surgery to the first contact with the clinic was 2 months, the median duration of follow-up was 2.8 months (0–16 months), and the median number of contacts was 3 (range 1–14).

2.4.1. PHARMACOLOGICAL PRINCIPLES

Pharmacokinetic and pharmacodynamic principles characterize the magnitude and time course of drug effect.⁶⁹ Pharmacokinetics describes what the body does to the drug—the processes of distribution and elimination (metabolism and excretion). For the drug to work, it needs to reach its target site (target molecule) at a sufficiently high concentration. The increase in concentration and the onset of action depend on the pharmacokinetic properties of each drug. Pharmacodynamics describes what the drug does to the body, the relationship between drug concentrations and its pharmacological effect, the mechanisms of action, and biochemical and physiological effects. The dynamic range is the concentration range where the drug effect occurs; levels below that are ineffective and those above that do not provide additional effect but increase the risk of adverse effects.

In finding the optimal regimen and dose, careful assessment of each patient's underlying condition must be recognized: age, body habitus, gender, chronic exposure to opioids, benzodiazepines, tobacco or alcohol use, presence of heart, lung, kidney, or liver disease, and the extent of blood loss or dehydration. The goal is personalized medicine, which in the future will likely make use of the knowledge of each patient's genetic coding for metabolism of analgesics and pain sensitivity.

2.4.2. ANALGESICS FOR POST-TONSILLECTOMY PAIN

2.4.2.1 *Paracetamol*

Paracetamol is used as the first line analgesic for mild to moderate acute postoperative pain, but in many cases, it is insufficient for pain control when used alone. It is a safe analgesic in moderate doses; it has minor anti-platelet activity and good gastrointestinal tolerance, but the potential for serious hepatic injury exists in high doses. Paracetamol is considered a centrally acting analgesic. The precise mechanism of action is unknown, and it may deliver analgesia through multiple dose-dependent mechanisms. Paracetamol is metabolized into AM404 in the liver.⁷¹ AM404 is a transient receptor potential vanilloid 1 (TRPV1/capsaicin) channel inactivator and low-affinity ligand of the cannabinoid-1 receptor; these receptors are involved in the analgesic effect of paracetamol.^{72,73} AM404 also reduces prostaglandin synthesis in activated microglia (central nervous system macrophages) by inhibiting cyclooxygenase (COX) activity; this effect seems to occur in higher paracetamol doses.⁷⁴ It has a weak anti-inflammatory effect and additive analgesic effect with NSAIDs.⁷⁰ Paracetamol has also been suggested to modify pain by reinforcing serotonergic descending inhibitory pain pathways.⁷⁵ For acute moderate to severe postoperative pain, a single dose of 1 g paracetamol offers at least 50% pain relief over 4–6 hours for 50% of adult patients; the number needed to treat (NNT) value is 3.5–5 (Figure 4).⁷⁴ For acute postoperative pain in pediatric patients, a single dose should be as high as 20–30 mg kg⁻¹ (in hospital 100 mg kg⁻¹ divided in 3–4 doses for 2 postoperative days and from then on 60 mg kg⁻¹ divided in 3–4 doses).^{77,78} For fever and pain (other than acute postoperative pain) at home, the recommended dose is much lower, 15 mg kg⁻¹ 1–3 times daily. For adults, the recommended dose is 0.5–1 g p.o. 3 times daily, maximum 3 g daily.

2.4.2.2. *Nonsteroidal anti-inflammatory drugs*

NSAIDs are effective analgesics that relieve pain and inflammation, but they also have serious adverse effects. NSAIDs relieve pain by inhibiting the activity of COX enzymes and the subsequent production of prostanoids, which are released in response to nociception, surgical trauma, and inflammation. Prostaglandin E2 and prostacyclin (PGI2) sensitize pain nerve terminals to pain caused by other inflammatory mediators (such as bradykinin and 5-HT) and physical agents.

There are at least two types of cyclooxygenase (COX) enzymes. The prostaglandins produced by the COX-1 enzyme are involved in the regulation of physiological events, for example platelets, endothelium, gastric mucosa, and kidney (e.g., thromboxane; platelet aggregating effect, prostacyclin; vasodilator effect and platelet aggregation

inhibition and PGE₂; gastric mucosal protective effect). COX-2 also has physiological functions (e.g., production of vasodilator and platelet aggregation inhibiting prostacyclin (PGI₂) in the endothelium), but it is mainly induced in response to inflammation (certain cytokines) and strong nociceptive stimulation, which then results in intense prostanoid synthesis.

Traditional non-selective NSAIDs inhibit both COX-1 and COX-2 enzymes. The inhibition of COX-1 prevents platelet aggregation and vasoconstriction prolonging bleeding time, which may increase postoperative bleeding (depending on the drug dose, serum level, and half-life).⁷⁹ By selective blocking of the COX-2 enzyme, the aim is to calm inflammation and related pain without affecting normal prostanoid-mediated functions in the body. COX-2 selective NSAIDs do not interfere with platelet function and thus do not affect the risk of bleeding with recommended doses. However, in the endothelium, vasodilator and platelet aggregation inhibiting prostacyclin (PGI₂) production is blocked, which may increase arterial thrombosis, for example risk of stroke and myocardial infarction. This adverse effect was noticed over the years, and several COX-2 inhibitors were taken off the market.⁸⁰ Tonsillectomy patients are usually healthy and young, without risk of cardiovascular complications, and therefore COX-2 inhibitors are usually suitable. In the Swedish guidelines, COX-2 inhibitors are a preferred choice for pediatric patients, and although they are not registered for children, they (mainly celecoxib) have been used clinically for many years in the major Swedish pediatric departments without problems.⁸¹ Other adverse effects of NSAIDs are gastrointestinal irritation, gastric ulcer provocation, anuria and hyperkalemia (in patients with renal disease, congestive heart failure, generalized arteriosclerosis or fluid imbalance), and risk of heart failure (increased by 10-fold in patients with cardiac disease). Contraindications include treatment with anticoagulants, kidney deficiency, gastric ulcer, severe hypertension, heart failure; relative contraindications are age > 70 years and coronary arterial disease. Celecoxib is contraindicated for patients with sulfa allergy due to its' sulphonamide structure.

The relationship between NSAIDs and the risk of PTH has been studied over the years with conflicting results—some systematic reviews have reported an increased risk of reoperation and some have not found differences.⁸⁻¹⁰ The latest Cochrane review on pediatric tonsillectomy (2013) concluded that insufficient data exist to exclude an increased risk of PTH; the use of traditional NSAIDs was associated with a non-significantly increased risk of reoperation.¹⁰ In recent pediatric guidelines, NSAIDs have been recommended to be used in moderate doses; patients need analgesia to be able to eat and drink, and paracetamol is not effective enough as a single drug.^{80,82,83}

Non-selective NSAIDs and COX-2 inhibitors have NNT values ranging from 1.5 to 4.5 (Figure 4). Individual studies on adult tonsillectomies have proved their efficacy; however, no systematic review has been performed before that in Study III. Studies on pediatric tonsillectomy patients have shown that NSAIDs combined

with paracetamol are as efficient as opioids combined with paracetamol at providing adequate analgesia after tonsillectomy.^{82,84} In Finland, available traditional non-selective NSAIDs on the market are diclofenac, indomethacin, ketorolac, ibuprofen, ketoprofen, and naproxen. Of the COX-2 inhibitors, three are available: etoricoxib and celecoxib, and parecoxib for intravenous (i.v.) use only.

2.4.2.3. Opioids

Opioids relieve pain by inhibiting opioid receptors in the spinal cord, middle brain, brainstem, cortex, and via peripheral opioid receptors activated by inflammation. Opioids are the most effective antinociceptive agent which can be administered by i.v., peroral (p.o.), subcutaneous, transdermal, or transmucosal routes, or as additives in regional anesthesia. Optimal analgesia can be achieved easily in hospital by titration of strong opioids such as morphine, oxycodone, and fentanyl. The weak opioids codeine and tramadol are used for the treatment of moderate to severe pain. However, adverse effects such as respiratory depression, nausea, urinary retention, constipation, ileus, and pruritus may prevent their use. Contraindications include severe broncho-pulmonary and neuromuscular diseases. Opioid antagonists (naloxone 0.01–0.02 mg kg⁻¹ i.v. every 2–3 minutes until response is achieved) can treat all opioid receptor mediated side effects, such as respiratory depression and itching. Neuroleptics (e.g. dehydrobenzperidol 0.5 mg i.v. or i.m.) are most effective in treating nausea, which also aim in opioid-induced confusion. Opioids increase reuptake of serotonin in synapses thus increasing risk for serotonin syndrome in case of concomitant use of serotonergic medications (SSRI and SNRI antidepressants, triptans, 5-HT₃ blockers).

Codeine is a prodrug of which 6–10% is metabolized through the cytochrome CYP2D6 enzyme into morphine, which provides its primary analgesic effect. Codeine is mostly used as a combination of 30 mg codeine and 500 mg paracetamol (Panacod®, Paramax-Cod®, Paracetamol-Codein®, Altermol®). The combination of 800–1000 mg paracetamol plus 60 mg codeine p.o. provides effective pain relief for acute postoperative pain with an NNT value of 2.2 (Figure 4). The maximum daily dose of codeine is 240 mg p.o. for adults.

Pain relief can be inadequate in individuals that carry inactive copies of the CYP2D6 genes, and codeine is not transformed into morphine (2–10% of Caucasian people).⁸⁶ Individuals that have an “ultrafast metabolism” have more than two normal copies of CYP2D genes, and in these individuals codeine is rapidly converted into morphine and signs of opioid toxicity such as respiratory depression may develop. Reports have been published that codeine given postoperatively has led to overdoses and deaths in pediatric tonsillectomy or adenotonsillectomy due to OSA syndrome, and the majority of these patients have been diagnosed with ultrafast

metabolization of CYP2D6.⁸⁷ Airway swelling after tonsil and/or adenoid surgery has been thought to be a contributory risk factor for the development of respiratory failure in pediatric sleep apnea patients, whose symptoms worsen immediately after surgery.⁸⁶ Simultaneously occurring opioid sensitivity induced by repetitive hypoxic periods, and decreased responsiveness to an increased partial pressure of carbon dioxide in the blood, predispose these patients to the risk of respiratory depression. If a patient is also a CYP2D6 ultrafast metabolizer, there is a real danger of respiratory arrest. Therefore the US Food and Drug Administration in 2017 and the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee in 2015 recommended avoiding (contraindicate) codeine in children younger than 12 years regardless of the surgery, and up to the age of 18 years in patients undergoing tonsillectomy or adenotonsillectomy for OSA syndrome.^{19,20} Codeine is also contraindicated for patients with biliary tract disease and acute asthma attack (may cause spasm of smooth muscle).

Tramadol has multiple mechanisms of action, including inhibition of the reuptake of serotonin (5-HT) and norepinephrine, and it stimulates the release of serotonin from presynaptic nerve terminals. The main active metabolite O-desmethyltramadol M1, which is produced by the CYP2D enzyme, binds with relatively high affinity to the μ -opioid receptor. Thus, opioid effects of tramadol are largely influenced by CYP2D6 activity, and this is similar with codeine. Following contraindication of codeine for pediatric tonsillectomy patients, tramadol use has increased, causing an increasing number of reports on opioid toxicity.²¹ In the United States, tramadol is also contraindicated (since 2017) for children less than 12 years regardless of surgery and in children less than 18 years after ear, nose, and throat surgery.²²

In Europe, tramadol is approved for use in children over 1–3 years for moderate to severe nociceptive pain management. The EMA and the European Society for Paediatric Anaesthesiology (ESPA) recommend restricting the use of tramadol for postoperative pain management in children with OSA syndrome and compromised respiratory function.^{23,24} ESPA guidelines nevertheless allow the use of tramadol for adenotonsillectomy inpatients if pain is severe despite the use of non-opioids, in which case appropriate minimal effective dosage must be determined individually by titration in the hospital setting where adequate monitoring is available (usually a maximum of 1 mg kg⁻¹ 1–3 times daily as needed). In order to determinate the genotype for tramadol metabolism a CYP2D6 gene test can be performed. For adults, the recommended dose is 50–100 mg p.o. 3–4 times daily. In our clinic, tramadol in moderate doses is used for adult patients with mild OSA (AHI < 15). Adverse effects of tramadol include dizziness, drowsiness, sweating, nausea, vomiting, dry mouth, and headache, which are more common and harmful for the elderly (overall incidence of 1.6% to 6.1%). Due to similar mechanisms of action and CYP2D6-mediated pharmacokinetic interactions, the use of tramadol with antidepressants should be carefully considered.

2.4.3. ADJUVANTS

2.4.3.1. *Dexamethasone*

The action of glucocorticoids is mediated through a cytoplasmic receptor. The activated glucocorticoid-receptor complex affects the expression of many genes, either by increasing or decreasing protein synthesis in cells.⁶⁷ Glucocorticoids reduce the production of several inflammatory factors and at the same time increase the synthesis of anti-inflammatory factors, which suppresses both the acute inflammatory response and the humoral and cell-mediated immune response, and leads to the suppression of the inflammation.⁶⁷ Glucocorticoids, particularly dexamethasone, are commonly used to reduce pain and PONV.^{89,90} Without PONV prophylaxis, the incidence is 35–75% in pediatric tonsillectomy.⁸⁷ A single dose of dexamethasone intraoperatively decreases postoperative pain, the need for rescue opioids, and PONV.^{91,92} A commonly used dose is 0.1–0.15 mg kg⁻¹ i.v. at the induction of anesthesia. An increased risk of PTH associated with the use of dexamethasone has been suspected in some small studies, but it has not been confirmed in systematic reviews and meta-analyses, although a recent systematic review and register study reported an increased risk of reoperation among pediatric patients but not among adults.¹⁵⁻¹⁸ Several guidelines recommend its use in children in moderate doses based on benefit over harm, including decreased throat pain, decreased PONV, and earlier resumption of oral intake, which is crucial in terms of hydration, especially when NSAIDs are used.^{6,81}

2.4.3.2. *Gabapentinoids*

Gabapentinoids (gabapentin and pregabalin) act by binding to $\alpha 1\delta$ and $\alpha 2\delta$ subunits of the voltage-gated Ca⁺⁺ channel in the presynaptic nerve terminals, inhibiting release of excitatory neurotransmitters, controlling the irritability of dorsal horn neurons and thus relieving and preventing the development of hyperalgesia. Gabapentinoids administered prior to surgery reduce postoperative pain, opioid requirements, and opioid-related adverse effects. Adverse events of gabapentinoids such as sedation and dizziness are observed in higher doses, but they are considered of minor importance in the case of intense pain in a postoperative setting. Recent systematic reviews, however, have questioned their efficacy (NNT has increased from 2–4 to 5–7).^{93,94} The disadvantage of gabapentinoids is the potential for misuse and addiction. Therefore, treatment decisions should be made on an individual basis. In the Helsinki University Hospital, if the type of surgery involves a high risk of chronic pain or nerve damage, pregabalin 75-150 mg 2 times daily starting in the

morning before surgery and continued for 2-4 weeks, is recommended. Pregabalin is eliminated by the kidneys, and in case of renal insufficiency, doses must be lower.

2.4.3.3. NMDA antagonists

Ketamine is an anesthetic drug that has been used as a general anesthetic from the 1970s, and in recent years in low doses as an adjuvant to analgesia. It causes a non-competitive dose-dependent blockade of the NMDA receptor and thereby inhibits development of central sensitization and hyperalgesia.⁶³ Low dose ketamine as boluses or infusion reduces postoperative pain.^{55,95,96} In pediatric tonsillectomies, a systematic review (2014) and studies published thereafter have reported that preoperative i.v. and peritonsillar ketamine locally provide pain relief for 24 hours without an increase in side effects.⁹⁷

Ketamine is used perioperatively in surgeries in which there is high risk for severe postoperative pain. The usual dose of esketamine (s - enantiomer of ketamine) is 10-25 mg i.v. bolus at the induction of anesthesia, followed by 2-5 mg h⁻¹ i.v. infusion (1 mg ml⁻¹) until the end of surgery, or continued into PACU. Postoperatively, if opioids have not been effective enough and tolerance and hyperalgesia have developed, esketamine 1-2.5 mg i.v. bolus repeated every 5-10 minutes or 25-50 mg p.o. 4-6 times daily mixed in juice (causes sores, erosion of enamel and tooth decay) is useful. Ketamine may cause adverse effects such as increased salivation, hallucinations, nightmares, nausea and vomiting, but in low doses for treatment of pain, adverse effects have not been problematic. Central nervous system adverse reactions may be reduced/prevented by combining ketamine with a small dose of a benzodiazepine such as diazepam or midazolam or an alpha-2 agonist such as clonidine or dexmedetomidine. Ketamine is contraindicated for patients for whom there is a serious risk of an increase in blood or cerebral pressure and with psychiatric disorders.

Dextromethorphan has been studied in recent years for adjuvant to opioid analgesia. It has been used an over-the-counter anti-tussive drug for decades. Dextromethorphan is an NMDA-receptor antagonist and has also many other neuropharmacological actions—among others, it increases serotonin levels in synapses. It is metabolized by the CYP2D6 enzyme. A qualitative systematic review of perioperative dextromethorphan for postoperative pain, including 28 studies of which three were tonsillectomy studies, reported a reduced need for opioids and a reduction in opioid-related adverse events especially when used parenterally, but clinical meaningfulness of the effect was not clear.⁹⁸ In a more recent meta-analysis that included 40 studies of which two were tonsillectomy, perioperative dextromethorphan was associated with a significant reduction in pain scores and postoperative opioid use for 24–48 hours following surgery.⁹⁹

2.4.3.4. Other adjuvants

Antihyperalgesic adjuvants magnesium, dexmedetomidine, and lidocaine as i.v. infusions are increasingly used and studied as part of multimodal analgesia in many surgical procedures.¹⁰⁰ So far, for post-tonsillectomy pain, the evidence of efficacy has been minimal or nonexistent.¹⁰¹ Magnesium is a weak NMDA antagonist which has been shown to reduce postoperative analgesic consumption and opioid-related adverse effects in orthopedic surgery when administered as i.v. infusion.¹⁰² Dexmedetomidine is a selective α_2 -agonists with analgesic, sedative, anxiolytic and sympatholytic effects.¹⁰¹ It potentiates the effect of opioids (synergistic interaction), and possibly development of tolerance. Sympatholytic effect results from decreased release of norepinephrine from sympathetic nerve endings. In addition to its analgesic effects, dexmedetomidine is commonly used as a sedative in the intensive care unit, for awake tracheal intubation with fiberscope, and nasally administered in sedation for minor operations especially in pediatric patients. Bradycardia is a common adverse effect and therefore monitoring is needed. Lidocaine is a common local anesthetic and antiarrhythmic drug which has been used in recent years as intravenous infusion for prevention of hyperalgesia and postoperative pain.^{55, 103} According to recent Cochrane review (2018) on continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults, clinically relevant effect was questionable later than 24 hours.¹⁰³

Analgesics and adjuvants for acute postoperative pain are listed in Table 1. Recommendation of post-tonsillectomy pain medication in adult and pediatric outpatients at the Helsinki University Hospital, Department of Otorhinolaryngology—Head and Neck Surgery are found in Appendix 2 and 3 respectively.

Table 1. Analgesics and adjuvants for acute postoperative pain. AV, atrioventricular; CNS, central nervous system; COX, cyclooxygenase; i.v., intravenous; NMDA, N-methyl-D-aspartate; OSA, obstructive sleep apnea; PACU, post-anesthesia care unit; p.o., perorally.

Analgesics, adjuvants	Mechanism of action	Usual dose in acute postoperative pain	Adverse effects	Contraindications
Paracetamol	Metabolism to AM404 → inhibition of COX in CNS → production of prostaglandins ↓ TRPV1/capsaicin channel inactivation Cannabinoid-1 receptor activation Serotonergic descending inhibitory pain pathways?	Adults: 0.5–1g x 1–3 p.o. /day Pediatric: 100 mg/kg p.o. /day for 2 days, followed by 60 mg/kg p.o. /day (divided in 3–4 doses)	Potential for serious hepatic injury in high single doses > 150/mg/kg	Liver insufficiency Do not combine with NSAIDs in longstanding use (risk of kidney failure)
NSAIDs - Traditional: Diclofenac, indomethacin, ketorolac, ibuprofen, ketoprofen, naproxen - COX-2 selective: etoricoxib, celecoxib, parecoxib	Inhibition of cyclooxygenase enzymes (COX) → production of prostaglandins ↓ (released in response to nociception, surgical trauma, inflammation)	Adults: Ibuprofen 600–800 mg x 3 p.o., dextketoprofen 50mg p.o. x 1–3/day Pediatric: Naproxen 5 mg/kg x 2 Ibuprofen 40 mg/kg/day (divided in 3 doses p.o./p.r.) Celecoxib?	- Gastrointestinal irritation and bleeding, gastric ulcer provocation - Anuria and hyperkalemia in patients with renal disease, congestive heart failure, generalized arteriosclerosis or fluid imbalance - In patients with cardiac disease, the risk of heart failure 10-fold increased	- Anticoagulants - Asthma (10% of patients) - Kidney deficiency - Gastric ulcer - Cardiovascular disease (depending on severity), generalized arterio-sclerosis - Fluid imbalance - Age above 70–75 years (relative)
Opioids: Oxycodone, codeine, tramadol	Opioid receptors (μ, δ, and κ) - in spinal cord, middle brain, brainstem and cortex - peripheral opioid receptors activated by inflammation	Adults: - Oxycodone 0.05mg/kg i.v., 0.07–0.13 mg/kg i.m., 5–15mg p.o., 30–50% less for elderly - Tramadol 50–100mg p.o. x 1–3/day - Paracetamol 500mg-codeine 30mg p.o. 1–2 x 3–4/day Pediatric: Oxycodone 0.05–0.1 mg/kg i.v., tramadol 1–2 mg/kg p.o. x 1–4/day	All: - Respiratory depression (dose-dependent), PONV, urinary retention, constipation, ileus, pruritus, addiction, endocrinological and immunological effects - Risk of serotonin syndrome with SSRI + SNRI antidepressants, triptans Tramadol: - Dizziness, drowsiness, sweating, nausea, vomiting, dry mouth, headache	All: - Severe broncho-pulmonary disease - Neuromuscular diseases - OSA (except tramadol if AHI < 15) Paracetamol-codeine + tramadol: - <12 years of age - 12–18 years of age if tonsillectomy for OSA - CYP2D6 ultra-fast metabolizer Paracetamol-codeine: Liver insufficiency, biliary tract disease, acute asthma attack
Dexamethasone	Glucocorticoid receptor in the in the cytoplasm in the cell → suppression of inflammation ↓	0.1–0.15 mg/kg i.v. at the induction of anesthesia	Elevation of blood glucose level, immunosuppression	Caution if diabetes, gastric or duodenal ulcer
Gabapentinoids: Pregabalin, gabapentin	α1δ and α2δ-subunits of voltage-gated Ca++ channel antagonist in the presynaptic nerve terminals in CNS → excitatory neurotransmitters ↓, irritability of dorsal horn neurons ↓, hyperalgesia ↓	Pregabalin: 75–150 mg p.o.x2/day for 2–4 weeks e.g. if the type of surgery involves a high risk of chronic pain or nerve damage	Fatigue, drowsiness, dizziness, headache, memory and speech disorders, paresthesia, ataxia, visual disturbances, dyspepsia, weight gain, peripheral edema not relieved by diuretics, addiction	Allergy
NMDA-antagonists: Ketamine (dextromethorphan under studies)	NMDA receptor antagonist, ketamine: hyperalgesia ↓	Esketamine: - At induction of anesthesia bolus 10–25 mg i.v. + infusion (1mg/ml) 2–5 mg/h i.v. - PACU: 1–2.5mg i.v. repeated every 5–10 min +/- infusion 2–5 ml/h (1mg/ml) i.v., or 25–50 mg p.o. x 4–6/day in juice	Ketamine: increased salivation, hallucinations, nightmares, nausea and vomiting are rare, when used in subanesthetic doses for pain (hallucinations may be reduced/prevented by combining with a small dose of a benzodiazepine such as diazepam or α2 agonists). Tooth decay	Patients for whom there is a serious risk of an increase in blood or cerebral pressure, psychiatric disorders
Magnesium	Weak NMDA antagonist, hyperalgesia ↓	i.v. infusion/ locally in regional anesthesia	Hypotension	Myasthenia gravis severe kidney deficiency
Lidocaine	Sodium channel blocker, immunosuppression, other mechanism? At therapeutic plasma levels (1–3 mg/l) alleviates various pain conditions. Hyperalgesia ↓	i.v. infusion/ locally in regional anesthesia	Hypotension, bradycardia	Allergy, many contraindications if used as infusion
α2 agonists: dexmedetomidine, clonidine	α2 agonists potentiate the effect of opioids (synergistic interaction), development of tolerance? Sympatholysis (inhibition of norepinephrine release from sympathetic nerve endings) Hyperalgesia ↓	i.v. infusion/ locally in regional anesthesia	Hypotension, bradycardia	AV block, uncontrolled hypotension, bradycardia, acute cerebrovascular accident

2. Review of literature

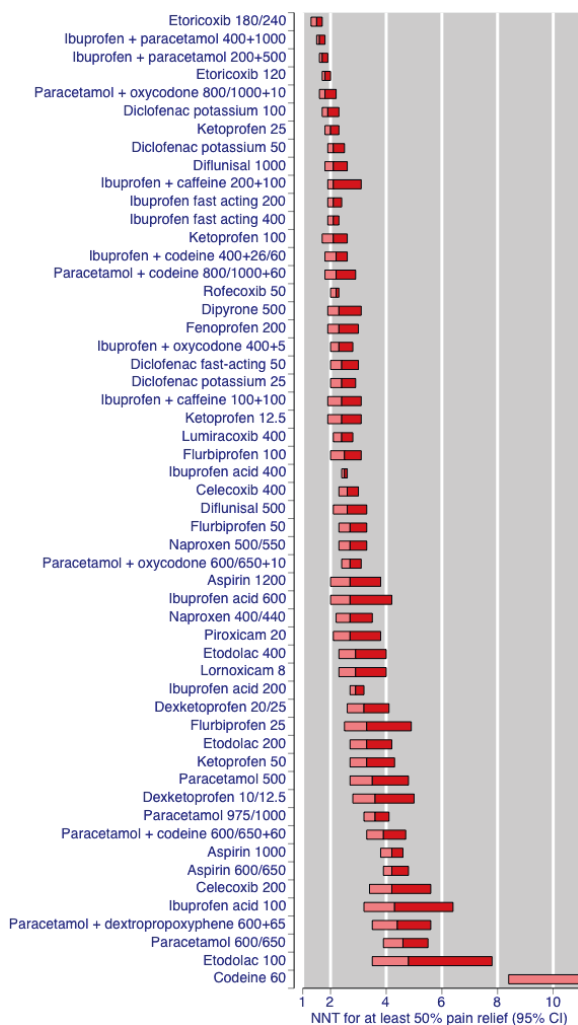


Figure 4. Single-dose analgesics for moderate to severe acute pain: NNT for at least 50% maximum pain relief over 4–6 hours. NNT, number needed to treat is a measurement of the impact of a medicine or therapy by estimating the number of patients that need to be treated in order to have an impact on one person. The higher the NNT, the less effective the treatment. Treatments with NNTs of 2–5 are considered effective for acute pain. Reproduced with permission from Moore RA, Derry S, Aldington D, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults – an overview of Cochrane reviews. Cochrane Database of Systematic Reviews 2015, 9. Art. No.: CD008659.

2.4.4. LOCAL ANESTHETICS

Local anesthetics provide regional anesthesia by producing a blockade of neuronal transmission when applied near the axons. Action potentials are blocked due to an inhibition of sodium (Na^+) flow through the Na^+ channel by direct blocking or influencing the Na^+ channel conformation.¹⁰⁴ Local anesthetics are usually weak bases ($\text{pK}_a = 7.6\text{--}9.0$) that are commercially prepared as an acidic solution, typically at pH 4–5 to ensure preservation. The pK_a defines the pH, where half of the drug is ionized (conjugate acid) and half is non-ionized (base). The non-ionized (base) form is more hydrophobic than the ionized form and penetrates the nerve membrane. If tissue is acidic (e.g., surgical site, inflammation), most of the local anesthetic is in its ionized (hydrophilic) form and does not pass through the nerve membrane, resulting in a weaker effect.¹⁰⁴ In clinical practice, sodium bicarbonate has been added to local anesthetics to increase the pH and the proportion of the membrane-penetrating lipid soluble form, and found to decrease the onset of the sensory blockade, although the magnitude of the effect is minimal (epidural anesthesia, peribulbar anesthesia).^{105,106}

Local anesthetics (lidocaine, bupivacaine, levobupivacaine, ropivacaine) have been studied as peritonsillar injection before tonsillectomy or topically with swabs soaked in local anesthetic after removal of tonsils; however, the evidence regarding the efficacy is minimal and of questionable meaningfulness.^{26,27} Topical anesthesia is considered safer than peritonsillar injection as no needle penetrates tissue. Adjuvants to local anesthetics in peripheral and regional nerve blocks, α_2 adrenergic receptor agonists (clonidine, dexmedetomidine), dexamethasone, and magnesium have been shown to prolong analgesia.^{97,107,108} A systematic review of adjuvants to local anesthetics in post-tonsillectomy pain (2017) reported strong evidence regarding the effect of magnesium (NMDA antagonist that has synergistic action with local anesthetics) and dexamethasone in the reduction of pain and analgesic requirement over 24 hours, and recommended their use.¹⁰⁹ Tramadol and meperidine did not have a similar effect on pain and analgesia. Current research on local anesthetics is now focusing on novel molecules with longer duration of action (e.g., butyl-amino-benzoate, an ester local anesthetic agent that has been shown to provide pain relief for up to 14 weeks by novel mechanisms such as blockade of Na^+ and K^+ channels), and delivery mechanisms for prolonged bioavailability, such as liposomal, microsphere, and cyclodextrin systems, which may provide safer perioperative care, and reduced opioid consumption and pain, while minimizing side effects.¹¹⁰

3. AIMS OF THE STUDY

The main purpose of the present work was to investigate immediate complications after tonsillectomy with emphasis on PTH, and the intensity of post-tonsillectomy pain. In addition, the aim was to evaluate the evidence of the effectiveness of systemic analgesics and dexamethasone for post-tonsillectomy pain, and whether topical ropivacaine is effective in the prevention of post-tonsillectomy pain.

The specific aims were:

1. To investigate the incidence of post-tonsillectomy complications (Studies I and II).
2. To investigate whether perioperative medication is associated with risk of complications (Studies I and II).
3. To assess the intensity of post-tonsillectomy pain (Studies III and IV).
4. To evaluate evidence of the analgesic effect of systemic analgesics and dexamethasone (Study III).
5. To investigate the efficacy of topical ropivacaine in preventing post-tonsillectomy pain (Study IV).

4. MATERIAL AND METHODS

4.1. PATIENTS

4.1.1. STUDIES I AND II

Studies I and II are retrospective chart reviews that analyzed the incidence of PTH in pediatric outpatients (Study I), the incidence of all postoperative complications of adult outpatients (Study II), and the association of those complications with perioperatively administered medications. Patients were operated for tonsillectomy with or without adenoidectomy during a 12-month period (between May 1, 2007 and April 30, 2008) at the Department of Otorhinolaryngology—Head and Neck Surgery, in Helsinki University Hospital. The exclusion criterion was tonsillectomy performed as part of a combined surgical procedure. In Study I, 842 adult patients (16 years or older) were included, and in Study II, 691 pediatric patients (1–16 years).

4.1.2. STUDY III

Study III is a systematic review and meta-analysis that evaluated evidence of efficacy, adverse effects, and the clinical value of systemic analgesics and dexamethasone used for post-tonsillectomy pain in adult and adolescent (≥ 13 years of age) patients. Double-blind placebo-controlled randomized studies were included. Studies of less than 10 participants in a group were excluded. Twenty-nine trials representing 1816 patients met the inclusion criteria (Figure 5).

4.1.3. STUDY IV

Study IV is a prospective, randomized double-blind study that investigated the effect of topical 1% ropivacaine on post-tonsillectomy pain in adult outpatient surgery patients during two postoperative weeks. 160 adult patients were enrolled, of which 6 were excluded on the day of surgery for various reasons (Figure 6) and 154 in total were included in the final analysis (78 patients in the study group and 76 patients in the control group). The inclusion criteria were suitability for an outpatient procedure and classification I to II of the American Society of Anesthesiologists (ASA). The exclusion criteria were peritonsillar abscess less than 2 weeks before surgery, suspected malignancy of the tonsils, coagulation disorder, regular use of

prescription pain medication or antidepressants, contraindications to the drugs on the study, inability to communicate in Finnish or Swedish, inability to use a numeric rating scale (NRS) to measure pain intensity, and lack of Internet access at home.

4.2. ETHICAL ISSUES

Studies I, II, and IV were approved by the Institutional Ethics Committee. Informed consent was obtained from every participant in Study IV before entering the study.

4.3. STUDY DESIGNS, PROTOCOLS, INTERVENTIONS, AND OUTCOME MEASURES

4.3.1. STUDIES I AND II

Data on demographics, postoperative diagnosis, operation time, perioperative systemic and local medications, and type of postoperative complications were collected from medical records during a 12-month period (between May 1, 2007 and April 30, 2008) in the Department of Otorhinolaryngology, Helsinki University Hospital, Finland. The use of peritonsillar infiltrations of local anesthetic (lidocaine 10 mg ml⁻¹) containing epinephrine 10 mg ml⁻¹ and/or packages dipped in bismuth subgallate paste (factor XII activator in coagulation cascade) were recorded. Postoperative bleeding episodes were classified according to the criteria of Windfuhr and Seehafer: Grade I = stopped spontaneously or after clot removal, Grade II = required direct pressure or minor electrocautery under local anesthesia, Grade III = reoperation under general anesthesia.¹¹¹ In Study II, complication was defined as any unplanned contact with the hospital's health-care professionals that resulted in medical treatment within one month postoperatively. Dehydration was diagnosed as reported in the medical record based on the clinical examination and infection as empirical antibiotic treatment due to clinical presentation, and pneumonia was diagnosed with clinical examination and chest x-ray. In both studies, the incidence of complications and their association with perioperative medication was analyzed.

4.3.2. STUDY III

Study III is a systematic review and meta-analysis that followed the PRISMA statement guideline in performing and reporting the review (Figure 5).¹¹² Databases were searched to identify published or ongoing trials: PubMed, Ovid Medline, Cochrane Library, ClinicalTrials.gov, and EudraCT and by hand searching

reference lists of included studies and reviews. Randomized, double-blind, placebo-controlled studies published from January 1980 to February 2017 reporting on pain intensity or use of rescue analgesia in English were included. The inclusion criteria of intervention were administration of systemic analgesics (paracetamol, NSAIDs, gabapentin, pregabalin, ketamine, dextromethorphan) or dexamethasone for the prevention or treatment of pain. The primary outcome was incidence and/or intensity of pain and the secondary outcomes were use of rescue analgesia and adverse effects. The methodological quality and potential bias of included studies was assessed by the Cochrane risk of bias tool and Oxford Quality Scoring Scale (only studies with a score ≥ 3 were included).¹¹³

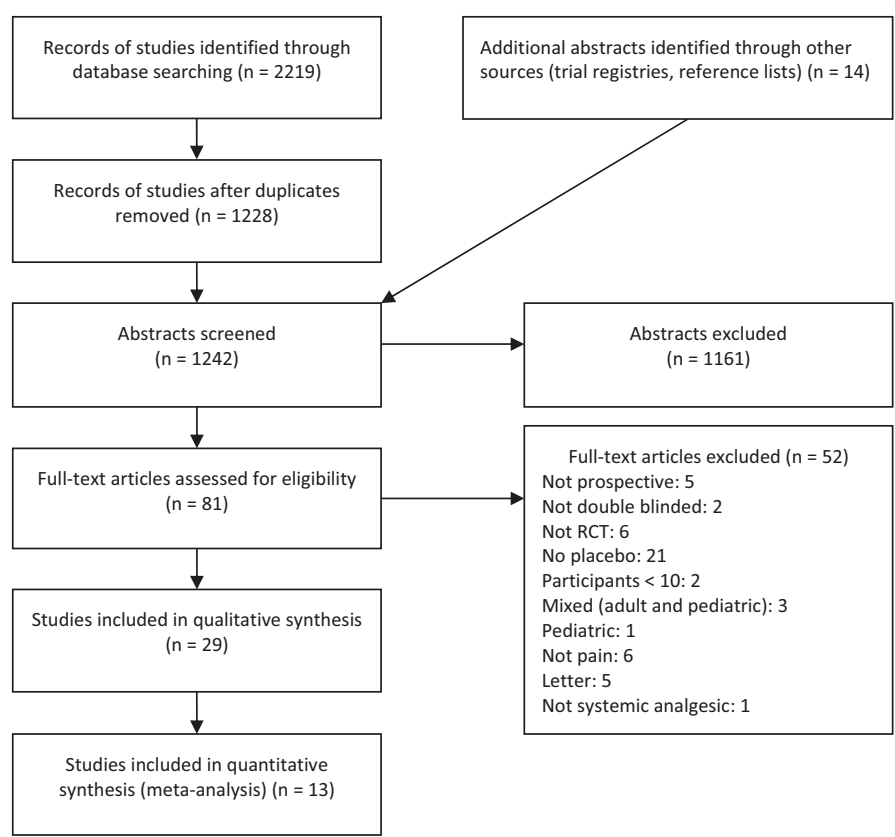


Figure 5. Flow chart of Study III. RCT, randomized controlled trial.

4.3.3. STUDY VI

Study VI is a prospective placebo-controlled randomized study. Patients were allocated into two study groups based on computer-generated randomization (Figure 6). As a premedication, all patients received 2 g paracetamol and, if necessary, 5 mg diazepam orally. Surgery was performed under standardized general anesthesia. Induction was performed with propofol ($3\text{--}5\text{ mg kg}^{-1}$), fentanyl (target $2.5\text{--}3\text{ }\mu\text{g kg}^{-1}$), and rocuronium ($0.3\text{--}0.5\text{ mg kg}^{-1}$). Dexamethasone $0.1\text{--}0.15\text{ mg kg}^{-1}$ i.v. (maximum 10 mg) at induction and tropisetron 2 mg i.v. at the end of surgery were administered for the prevention of PONV. Tonsillectomy was performed with cold instruments and hemostasis with bipolar forceps and compression with swabs. At the end of surgery after hemostasis, patients received ketoprofen $1\text{--}2\text{ mg kg}^{-1}$ i.v. (target 1.5 mg kg^{-1} ideal body weight, maximum 100 mg) for the prevention of postoperative pain. A nurse unaffiliated with the study prepared a syringe with either ropivacaine (Naropin®, B. Braun) or NaCl 0.9% according to the computer-generated randomization list made by a pharmacist at the hospital pharmacy. Liquid was then injected into a sterile steel cup containing four small swabs, which were then squeezed to remove excess fluid. At the end of surgery, two swabs were tightly packed into each tonsillar bed for 5 minutes.

Postoperative pain intensity using NRS (range 0–10) and adverse effects were recorded every 10 minutes in the post-anesthesia care unit (PACU) and at the Outpatient Surgery Unit every hour until discharge. If pain was measured at rest (NRSr) > 3 or on swallowing (NRSs) > 5 , oxycodone (0.05 mg kg^{-1} i.v.) was administered as a rescue analgesic in the PACU, or one tablet of a combination of paracetamol (500 mg) and codeine (30 mg) (Panacod®) in the Outpatient Surgery Unit. At discharge, patients received 600 mg tablets of ibuprofen to be used 3 times daily regularly during the first week and thereafter as needed for 2 weeks, and one or two tablets of Panacod® 3–4 times daily during the first 2–3 postoperative days and thereafter as needed for 2 weeks. For 2 weeks, patients completed a secured web-based electronic questionnaire every day on intensity of pain and other symptoms from the previous 24 hours (Appendix 1). Data on patient age, weight, height, smoking, ASA classification, postoperative NRSs and NRSr values, rescue analgesia, and adverse events during the perioperative period, and postoperative complications were collected from each patient's medical records. Bleeding episodes were classified according to the criteria proposed by Windfuhr and Seehafer.¹¹¹

The primary outcome was NRS on swallowing (NRSs) on postoperative days 1–7. The secondary endpoints were worst pain during the 2-hour follow-up in the PACU, NRSs and NRSr during the second postoperative week, and the number of ibuprofen and paracetamol-codeine tablets consumed during the 2-week follow-up.

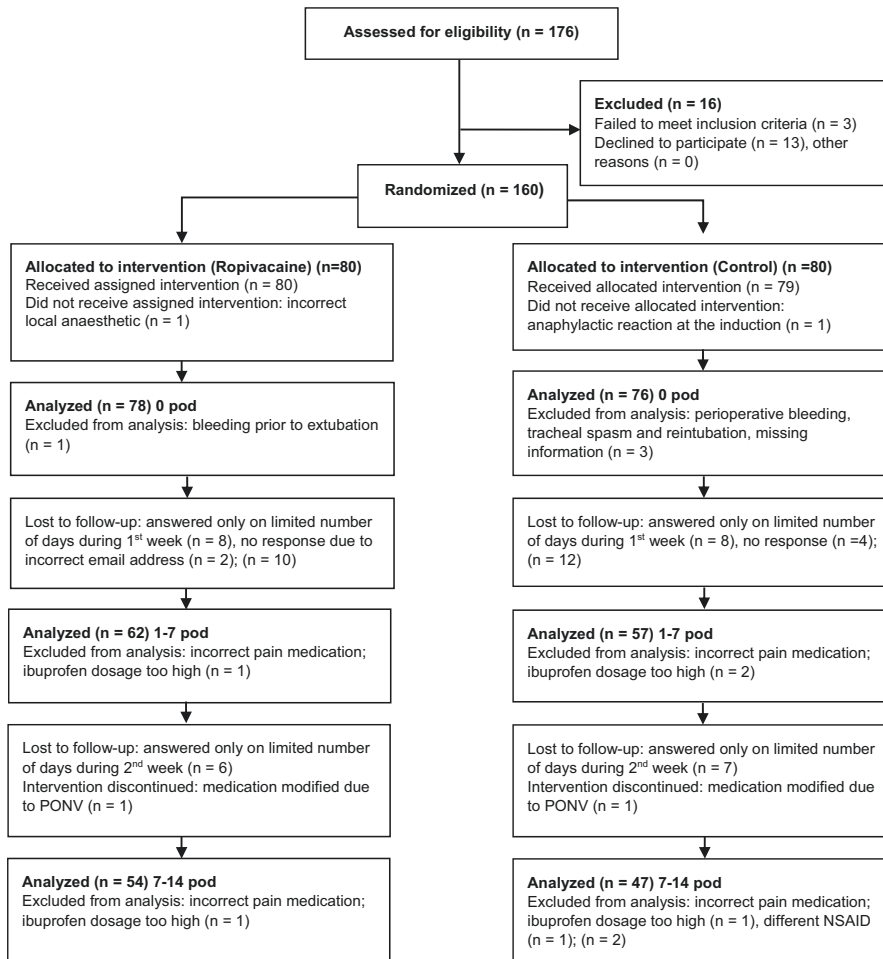


Figure 6. Flow chart of Study IV. NSAID, nonsteroidal anti-inflammatory drug; Pod; postoperative day; PONV, postoperative nausea and vomiting.

4.4. STATISTICS

4.4.1. STATISTICAL METHODS

In Studies I, II, and III, continuous data were presented as the median with standard deviation (SD) and 95% confidence interval (CI), and in Study IV as the median with interquartile range (IQR) and 95% CI, and categorical data as mean with range. Continuous data were analyzed by performing statistical analyses with the Mann–Whitney *U*-test and categorical data by the Pearson χ^2 test in all studies. Statistical

significance was set at a p value of < 0.05 , and the Bonferroni correction was used for adjustment of the p value in the multiple comparison situation (Study IV).

Study I investigated the incidence of PTH, and Study II the incidence of all postoperative complications. Both studies investigated the association of complications with perioperative medication, reported as the odds ratio (OR) with 95% CI. We used IBM SPSS Statistics 22 to perform statistical analysis and Confidence interval analysis software v. 2.1.2 (Trevor Bryant, London, UK) for the CI limit of difference. Multicollinearity and confounding factors were analyzed with regression analysis (Study II).

In Study III data were analyzed quantitatively in a meta-analysis when a group of studies in which clinical heterogeneity was sufficiently small could be identified. Meta-analysis was carried out with Review Manager (RevMan) v. 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). If clinical heterogeneity was too great, data were analyzed qualitatively. We used “no more than mild pain” (less than 3/10 on the pain scale) as an acceptable result in clinical practice.¹¹⁴

In Study IV, area under curve (AUC) was plotted for the daily NRS values for each patient during the follow-up time (single value per patient) and compared between groups to assess the treatment effect, reflecting pain burden better than single values of groups per day. We measured adverse effects during the follow-up of 1–14 days postoperatively (questionnaires), also expressed as AUC. We used NCSS 8 (www.ncss.com) for statistical analyses, Confidence interval analysis software v. 2.2.0 for the CI limit of difference, and the electronic questionnaire provided by Eduix (Tampere, Finland).

4.4.2. POWER ANALYSIS

A power analysis was performed in prospective Study IV. We considered a 30% reduction in pain intensity (primary outcome NRSs in the first postoperative week) as a significant change. Using the results from a study on post-tonsillectomy pain (Akural et al.), the average (median) estimated AUC value for NRSs during the first postoperative week for the control group was 30 (IQR 24–39).¹¹⁵ To attain a power of 90% ($1-\beta$) and a significance level of 0.05 (α -error), we calculated that to demonstrate a 30% reduction in NRSs during the first postoperative week would require a patient population of 31 samples per group. We recruited 80 patients for each study group to compensate for potential dropouts and incomplete answers.

5. RESULTS

5.1 CHARACTERISTICS OF PATIENTS IN STUDIES I, II, IV

The main characteristics of Studies I, II, and IV are summarized in Table 2. In Study I on adult patients, 863 patients were operated on during the one-year study period, of which 21 patients were excluded due to combined surgical procedure. The diagnosis was chronic tonsillitis in 76% of cases, and tonsillar hypertrophy with or without adenoid hypertrophy in 15% of cases. In Study II on pediatric patients, 694 patients were operated on during the study period. Three tonsillectomies were performed in combination with neck cyst removal and were excluded. The diagnosis was tonsillar hypertrophy in 69% of cases and chronic tonsillitis in 14% of cases. In Study IV, 5 patients were excluded on the day of operation due to protocol violation and one patient due to anaphylactic reaction at the induction of anesthesia; 154 patients (78 patients in the ropivacaine group and 76 in the control group) were included (Table 2, Figure 6). During the first week, 120 patients (75%) provided complete results, including analgesics used according to instructions and the daily completion and return of questionnaires, and 101 patients (63%) during the second week. The protocol violations and the dropouts due to adverse effects (e.g., PONV or constipation) were associated with the rescue analgesic (codeine), not with the intervention.

Table 2. Patient characteristics. Categorical variables appear as a number and percentage; continuous variables appear as median and range. ASA, American Society of Anesthesiologists; TE, tonsillectomy; TEA, adenotonsillectomy.

Patient characteristics	Study I (n=842)	Study II (n= 691)	Study IV intervention (n=78)	Study IV control (n=76)
Age, years, median (range)	32 (16–86)	7 (1–16)	25 (18–47)	27 (18–59)
Female/Male, n (%)	495 (59) / 347 (41)	338 (54) /353 (51)	35 (56) / 27 (44)	36 (63) /21 (37)
ASA I/II/III, %	73/23/4	86/13/3	80/20/0	77/33/0
TE/TEA, %	94/6	39/61	100	100
Duration of operation, minutes, median (range)	24 (4–165)	23 (3–88)	22 (9–40)	20 (7–50)

5.2. RESULTS OF STUDIES I AND II

5.2.1. INCIDENCE OF POSTOPERATIVE COMPLICATIONS

Secondary PTH was the most common complication in both Studies I and II, occurring on postoperative days 5–8 (Figures 7a and 7b, respectively). In adults, the incidence of PTH was 14.5% (primary PTH 1.3%, secondary PTH 13%, reoperation 1.5%), and 4.1% of patients experienced several episodes of PTH. In pediatric patients, the incidence of PTH was 7.1% (primary PTH 0.6%, secondary PTH 6.5%, reoperation 4.2%), 7 patients (1%) experienced several episodes of PTH and 5 patients (0.7%) required red blood cell transfusion due to secondary PTH. In pediatric patients, the overall incidence of unplanned contacts was 14% (revisits 10%, readmission 8%, pain 3%, fever 2.3%, and PONV 1%).

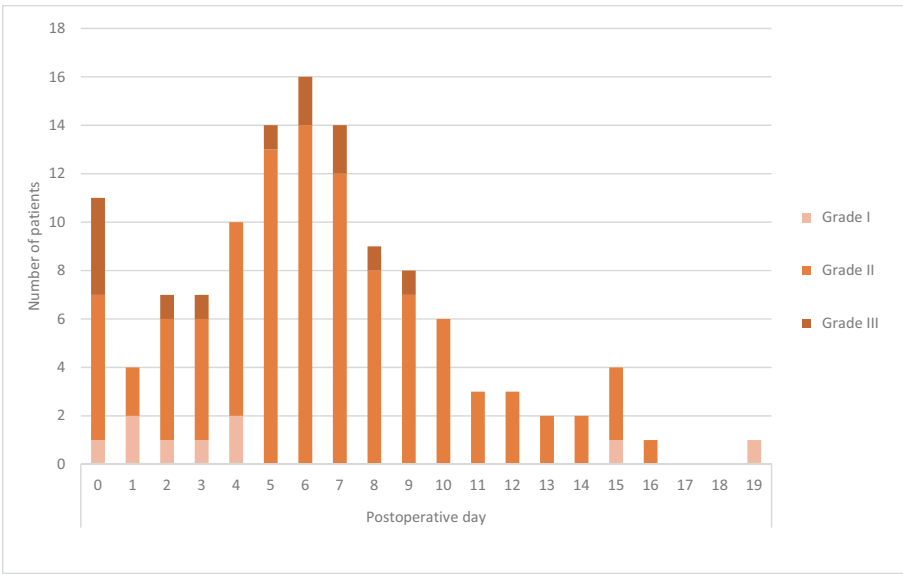


Figure 7a. Study I, adults (n = 842). Number of patients with post-tonsillectomy hemorrhage according to bleeding category and postoperative day. Bleeding category: Grade I = stopped spontaneously or after clot removal, Grade II = required direct pressure or minor electrocautery under local anesthesia, Grade III = reoperation under general anesthesia. If a patient experienced several bleeding episodes, only the first one was included.

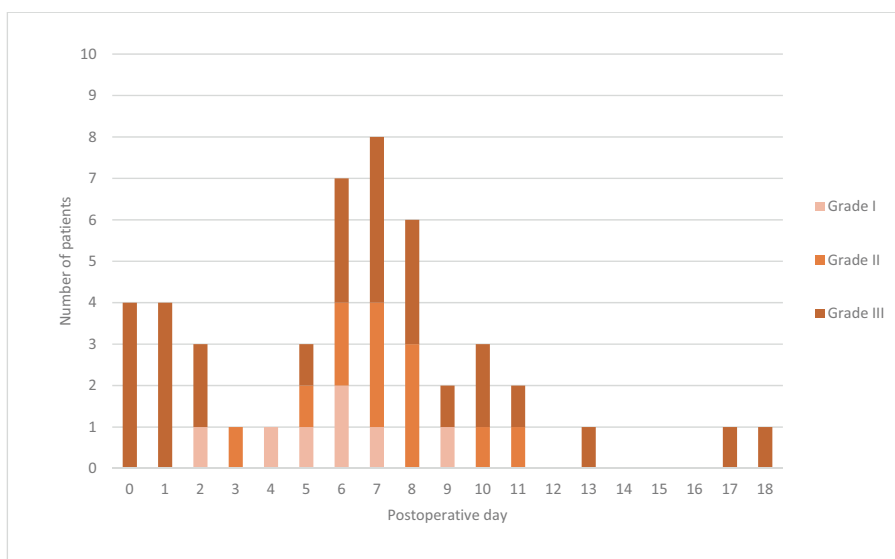


Figure 7b. Study II, pediatric patients (n = 691). Number of patients with post-tonsillectomy hemorrhage according to bleeding category and postoperative day. Bleeding category: Grade I = stopped spontaneously or after clot removal, Grade II = required direct pressure or minor electrocautery under local anesthesia, Grade III = reoperation under general anesthesia. If a patient experienced several bleeding episodes, only the first one was included.

5.2.2. ASSOCIATION OF PERIOPERATIVE MEDICATION WITH COMPLICATIONS

NSAIDs, opioids, 5-HT receptor antagonists, or dexamethasone were not associated with an increased risk of complications in either the pediatric or adult population. In Study II, local anesthesia (peritonsillar infiltration with lidocaine with epinephrine) used for 130 patients (19%) was associated with an increased risk of secondary PTH (14% vs. 4%, $p < 0.001$, OR 4), as well as the combination of lidocaine with epinephrine and bismuth subgallate (19% vs. 3%, $p < 0.001$, OR 7) which was used for 47 (7%) patients (Figure 8). Bismuth subgallate alone (9% of patients) was not associated with a risk of PTH.

To evaluate the impact of surgeons on the risk of PTH, they were divided into two categories based on their individual risk: $< 14\%$ risk of PTH (39 surgeons, Group 1) and $> 14\%$ risk of PTH (4 surgeons, Group 2). The use of local agents was more common in Group 2 (58% of patients) than in Group 1 (28% of patients). When no local agents were used, the risk of PTH was similar in both groups (Group 1: 3.6%, Group 2: 4.4%). In Group 2, patients that received lidocaine with epinephrine, the risk of PTH was higher than among those that had not received any local agents (24.6% vs. 4.4%, $p = 0.001$), whereas in Group 1 the difference was not significant (7.1% vs. 3.6%, $p < 0.45$). Significantly, an increased risk was found in Group 2 again for the combination of lidocaine with epinephrine and bismuth subgallate

5. Results

compared with those that did not receive any local anesthetic or hemostatic agents (24.1% vs. 4.4%, $p < 0.001$) (1 out of 2 surgeons); in Group 1 the difference was not significant (11.1% vs. 3.6%, $p = 0.35$) (2 out of 12 surgeons).

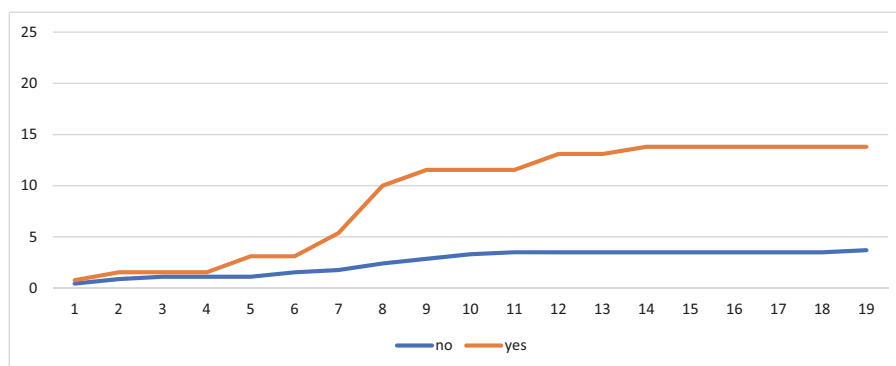


Figure 8. Cumulative proportion of post-tonsillectomy hemorrhage events among all patients (1–16 years of age) in relation to peritonsillar infiltration of lidocaine with epinephrine (yes) or without (no). Proportion appears as percentage (%).

5.3. RESULTS OF STUDY IV

5.3.1. PAIN INTENSITY ON THE DAY OF OPERATION AND NEED FOR RESCUE MEDICATION

Topical ropivacaine did not influence peak pain intensity values in the PACU (NRSs or NRSr) (median [IQR] 5 (3) ropivacaine, 5 (3) control, $p = 0.54$), or consumption of oxycodone in the PACU (median [IQR] 3 mg (4) ropivacaine, 3 mg (5) control, $p = 0.56$).

5.3.2. PAIN INTENSITY DURING THE FIRST AND SECOND WEEK AND CONSUMPTION OF ANALGESICS

The mean pain intensity on swallowing (NRSs) was moderate to severe on postoperative days 1–9 in the study group and on days 1–10 in the control group despite regular use of ibuprofen and the paracetamol-codeine combination (NRSs, NRSr). Topical ropivacaine failed to reduce NRSs during the first postoperative week ($p = 0.77$) (primary outcome), and the difference did not reach significance on the second week either ($p = 0.05$) (Figure 9a). Consumption of paracetamol-codeine tablets was significantly lower in the study group on the second postoperative week ($p = 0.006$) (Figure 9b).

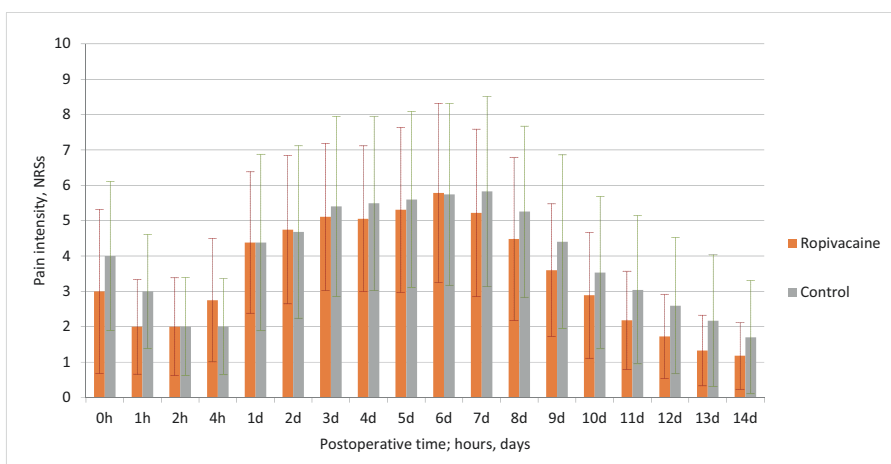


Figure 9a. Pain intensity on swallowing (NRSs) during the 2-week follow-up (0–4 hours and 1–14 days postoperatively). Variables appear as mean and standard deviation. NRSs, numeric rating scale on swallowing.

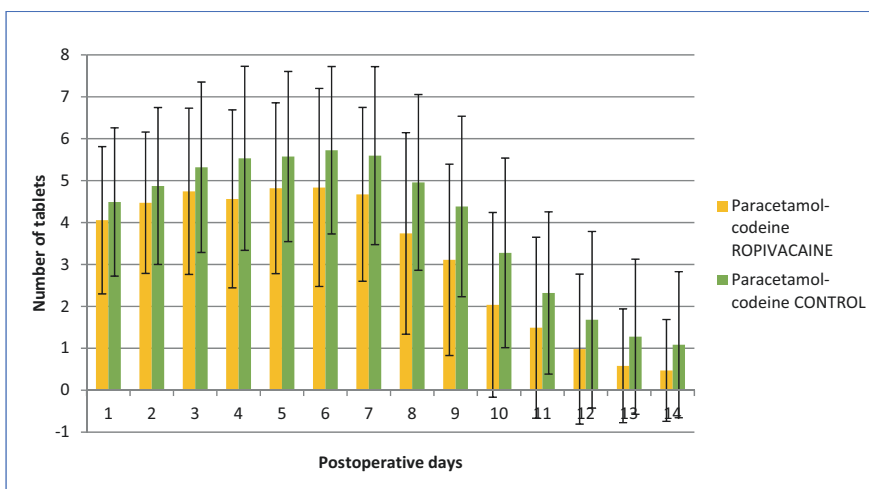


Figure 9b. Daily number of paracetamol-codeine tablets consumed during the 2-week follow-up (1–14 days postoperatively). Variables appear as mean and standard deviation.

5.3.3. ADVERSE EVENTS

78% of patients in the ropivacaine group and 68% in the control group experienced feelings of numbness in the throat in the PACU ($p = 0.24$). There was no difference in the incidence of PONV either (18% ropivacaine group, 20% control group, $p = 0.78$). Data from the questionnaires at 2 weeks, or medical records at one month postoperatively, did not reveal differences in the risk of overall complications including the risk of PTH, although in sub-analysis Grade II PTH (hemostasis under

local anesthesia) in the study group was more common compared with the control group (18% vs. 8%, $p = 0.048$).

5.4. RESULTS OF STUDY III

5.4.1. CHARACTERISTICS OF INCLUDED STUDIES

The systematic review included 29 randomized, double-blind, placebo-controlled studies representing 1816 patients, of which 9 could be combined in a pooled meta-analysis. Two studies compared paracetamol, 9 NSAIDs, 10 dexamethasone, 3 gabapentin, 1 pregabalin, 2 dextromethorphan, 1 ketamine, and 1 oxycodone. There were 17 single-dose and 12 multiple-dose studies. The duration of follow-up ranged from 70 minutes to 10 days; in most studies it was 24 hours or less. Pain intensity was the primary outcome in 11 studies, rescue analgesia in 6, and 12 studies did not specify the primary outcome, presenting a risk of bias. The main finding was the scarcity of data and short duration of studies that investigated analgesics for post-tonsillectomy pain, which is clinically relevant considering the number of tonsillectomies performed yearly and the intensity of pain following the procedure (Table 3).

Table 3. Reported pain intensity values during follow-up time. pod; post-operative day, NSAIDs; non-inflammatory agents, * = pain intensity values not available;
▲ = pain relief; ■ = VAS/VRS/NRS, ○ = VASs/VRsSs/NRSs; ● = VASr/VRsr/NRSr and VASs/VRsSs/NRSs.

Studies	1h	2h	4h	12h	24h	2pod	3pod	4pod	5pod	6pod	7pod	8pod	9pod	10pod
Paracetamol														
Atef 2008	●	●	●		●									
Salonen 2009	●	●	●											
NSAIDs														
Parker 1986, ibuprofen, acetylsalicylic acid	▲	▲	▲		▲	▲	▲	▲	▲					
Rorarius 1993, indometacin, diclofenac	*	*												
Tarkkila 1999, ketoprofen		●			●									
Salonen 2001, ketoprofen	●	●	●		●									
Naesh 2005, rofecoxib			■	■	■									
Ismail 2010, lornoxicam	●	●	●	●	●									
Mowafi 2011, lornoxicam	●	●	●	●	●									
Xie 2012, parecoxib	●	●	●	●	●									
Ng 2017, celecoxib					●	●	●	●	●	●	●	●		
Dexamethasone														
Fields 1994			■	■	■	■	■	■	■	■	■			
Carr 1999					○	○	○	○	○	○	○	○	○	○
Stewart 2002				○	○	○	○	○	○	○	○	○	○	
Al-Shehri 2004					■	■	■	■	■	■	■	■	■	
Rujirojindakul 2008	■		■		■	■								
Lachance 2008				○	○	○	○	○	○	○				
Vaiman 2011					○									
Vaiman 2011					○									
Thimmasettaiah 2012				■	■									
Khafagy 2013					■		■	■	■	■	■			
Gabapentinoids														
Mikkelsen 2006, gabapentin			●		●	●	●	●	●					
Jeon 2009, gabapentin	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Abdelmageed 2010, gabapentin	■			■	■									
Mathiesen 2011, pregabalin		●	●		●									
NMDA-antagonists														
Kawamata 1998, dextrometorphan	●				●	●	●	●		●				
Rafiei 2012, dextrometorphan					●									
Van Elstraete 2004, ketamine	●	●	●	●	●									
Opioids														
Vaiman 2012, oxycodone					○									

5.4.2. POST-TONSILLECTOMY PAIN AND ANALGESIA

The mean pain intensities were moderate to severe after tonsillectomy for 1–2 weeks among adult patients in both the placebo and treatment groups (Figures 10a and 10b).

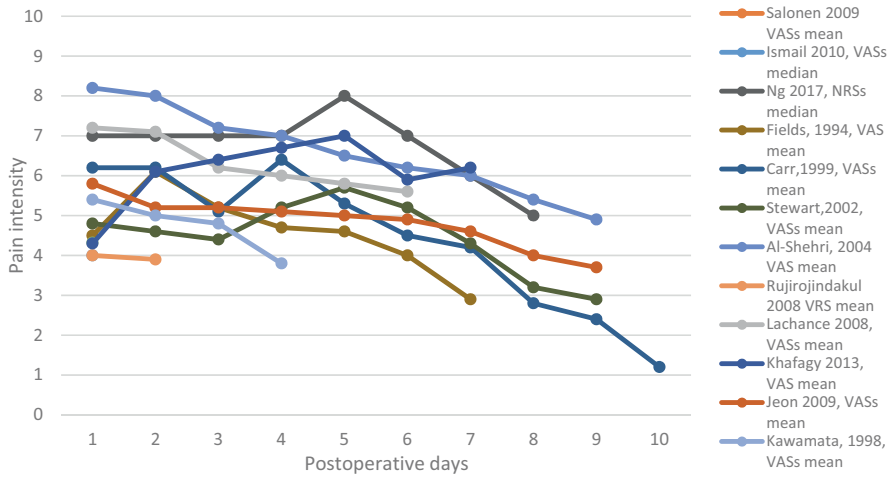


Figure 10a. Pain intensity in placebo groups on postoperative days 1–10. NRSs, numeric rating scale on swallowing; VAS, visual analog scale; VRS, visual rating scale.

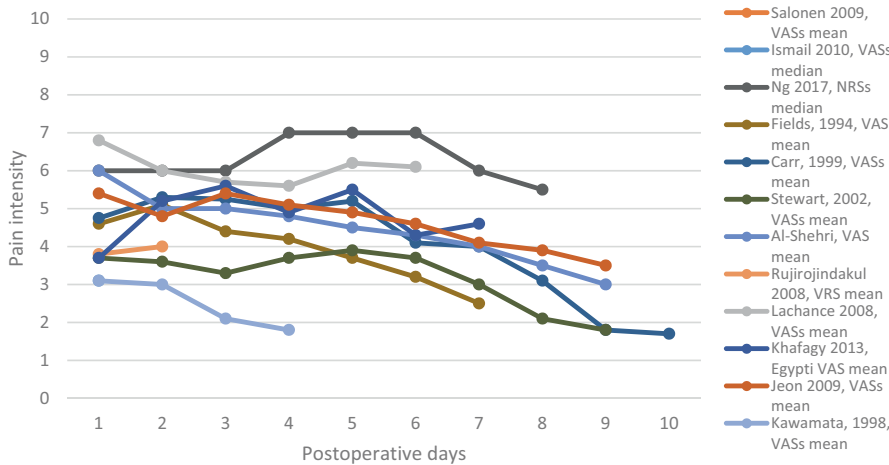


Figure 10b. Pain intensity (pain intensity or pain in swallowing) in the treatment groups on postoperative days 1–10. NRSs, numeric rating scale on swallowing; VAS, visual analog scale; VRS, visual rating scale.

Paracetamol (single dose of 2 g i.v. intraoperatively and multiple doses up to 4 g i.v. on the day of operation) showed a significant decrease in pain intensity (visual analog scale on swallowing) at 4 hours equivalent to an 18% reduction [-0.88 , $p < 0.03$], but no more at 24 hours, and decreased the need for opioids within 24 hours.^{116,117}

All NSAIDs (ketoprofen, ibuprofen, acetylsalicylic acid, diclofenac, indomethacin, lornoxicam, parecoxib, rofecoxib) reduced pain intensity or the need for opioids or both within 24 hours; one study on celecoxib for 10 postoperative days did not have any analgesic effect.¹¹⁶⁻¹²⁴ In all studies, the majority of patients needed rescue analgesics, indicating that NSAIDs alone do not provide adequate analgesia for tonsillectomy patients. Meta-analysis was possible only for two studies on ketoprofen, which failed to decrease pain intensity at 2 hours and at 24 hours ($p = 0.21$, $p = 0.13$, respectively); however, the need for rescue analgesics within 24 hours was reduced (Figure 11).^{116,117} Dexamethasone reduced pain intensity or the need for rescue analgesics in all 10 studies.¹²⁷⁻¹³⁶ In the pooled analysis, a single intraoperative dose of dexamethasone decreased pain intensity equivalent to 23% at 4 hours (-1.40 , $p < 0.001$) but no longer at 24 hours ($p = 0.05$) (Figure 11). Reduction of pain intensity lasted beyond the first postoperative day in all three multiple-dose studies and in one single-dose study. In the pooled analysis, gabapentinoids decreased pain intensity equivalent to 30% at 4 hours (-1.58 , $p < 0.001$) and 13% at 24 hours (-1.03 , $p < 0.001$) (Figure 11).¹³⁷⁻¹³⁹

Gabapentin 300–2400 mg p.o. on the day of operation reduced the need for rescue analgesics within 24 hours and preoperative pregabalin 300 mg within 4 hours. Dextromethorphan 45 mg p.o. preoperatively reduced pain intensity within 24 hours and the total dose of rescue analgesics within 24 hours in both included studies and in the other study for 6 postoperative days.^{141,142} Ketamine 0.5 mg kg^{-1} i.v. bolus with 2 $\mu\text{g kg}^{-1} \text{min}^{-1}$ i.v. infusion intraoperatively failed to show an analgesic effect.¹⁴³

Oxycodone 2 mg h^{-1} (14 mg) i.v. infusion during 16–23 hours postoperatively decreased pain intensity at 24 hours as expected.¹⁴⁴ In summary, when any of the analgesics or dexamethasone were used alone, the analgesic effect did not reach clinical meaningfulness due to the high pain intensity.

5. Results

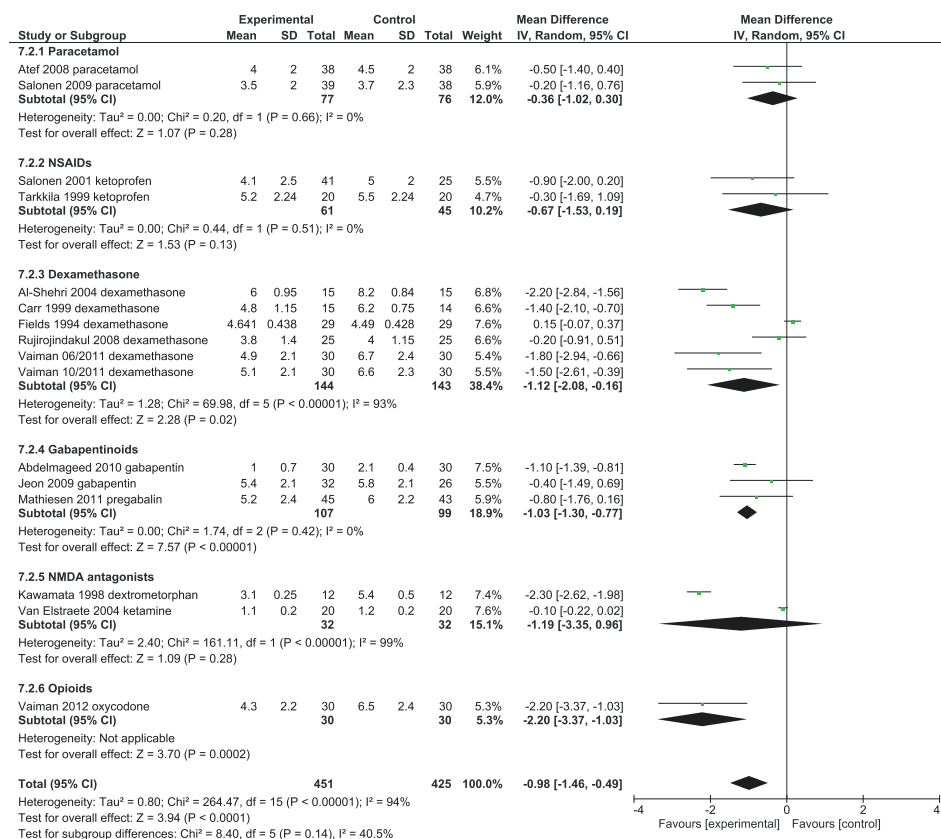


Figure 11. Forest plot showing the effect of perioperatively administered analgesics and dexamethasone on pain intensity at 24 hours. Pain intensity values (scale 0–10) with confidence intervals (CIs). Data evaluated using a random effects model. NMDA, N-methyl-D-aspartate; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation.

5.4.3. ADVERSE EVENTS

The incidence of PTH was reported in the paracetamol, NSAID, and dexamethasone studies, in which the risk of PTH was not increased. Dexamethasone reduced PONV during 24–48 hours postoperatively (risk ratio, RR 0.41, $p < 0.001$), reflecting an antiemetic and maybe also opioid-sparing effect. Gabapentinoids decreased postoperative vomiting also (RR 0.55, $p = 0.03$); however, in one study with high and multiple doses of gabapentin, adverse events were common. Dextromethorphan or ketamine studies did not report an increased risk of adverse events. Serious adverse events were reported in none of the included studies.

6. DISCUSSION

6.1. INCIDENCE OF COMPLICATIONS

In the retrospective Study II in pediatric patients, 14% of patients contacted hospital, 10% visited physician and 8% were admitted to the ward, 7.1% due to PTH, 3% due to pain; these results are in line with literature, somewhat less than in the previous prospective study in our clinic (17%).^{28,34,36}

In Study II, the incidence of primary PTH was 0.6% and secondary PTH 6.5%, and reoperation under general anesthesia (Grade III PTH) was required for 4.2% of patients (needed for smaller children which increases the incidence of reoperation rate). In Study I in adults, the incidence of PTH was 14.5% (primary PTH 1.3%, secondary PTH 13.2%, reoperation 1.5%). In the prospective Study IV, the overall incidence of PTH was 21%. In the ropivacaine group, the risk of Grade II PTH was significantly higher—18% vs. 8% ($p = 0.048$, 95% CI of difference 0–21%), but when compared with Study I, the incidence of PTH (14.5%) was within the same range; and may due to chance and the difference was barely significant with wide confidence interval, however, the effect of ropivacaine on the risk of PTH cannot be excluded. Questionnaires revealed that in both groups almost 50% of the patients reported blood in saliva, and more than 20% reported clear blood (from the surgical site), which describes the situation at home and highlights the fact that the incidence of PTH is much more common than previously thought. Patients are given instruction that bleeding usually ceases by itself in few minutes and to contact the unit that treated the patient, or an emergency unit after office hours, if the possible bleeding of the throat does not cease within 10–15 minutes. Some patients tolerate the recovery process better, whereas others contact the hospital more easily.

Patient education is of utmost importance, as the surgery carries risk of very rare but serious complications. Most patients are operated as outpatients, leaving the hospital on the day of operation, on the condition that they have company overnight and stay within one hour's reach of hospital in case they need to come back. Outpatient tonsillectomy has been proven to be safe, and it is more convenient for patients and caregivers; however, patient selection is important.

6.2. RISK OF POST-TONSILLECTOMY HEMORRHAGE

The studies confirmed the previously reported predispositions to PTH—older age and male gender—after tonsillectomy. In our studies, the incidence of PTH was

higher among adult patients (14.5%) than in pediatric patients (7.1%). Indication for surgery was not an independent risk factor for PTH.

Peritonsillar infiltration of lidocaine with epinephrine was commonly used among pediatric patients and was found to increase the risk of secondary PTH. Increased risk of PTH was associated with the use of systemic hemostatic or local hemostatic and anesthetic agents in both Studies I and II, but these agents are not used commonly in adult patients, so the numbers were small and separate statistical analyses were not possible in Study I. In Study II, local peritonsillar infiltration of lidocaine with epinephrine was used for 130 pediatric patients (19%) and it was associated with increased risk of secondary PTH (14% vs. 4%, $p < 0.001$, OR 4). Also, a combination of lidocaine with epinephrine and topical bismuth subgallate (used for 7% of patients), increased the risk of PTH (19% vs. 3%, $p < 0.001$, OR 7). Bismuth subgallate alone was not associated with a risk of PTH. To evaluate the impact of surgeons on the risk of PTH, they were divided into two categories based on their individual risk: $< 14\%$ risk of PTH (39 surgeons, Group 1) and $> 14\%$ risk of PTH (4 surgeons, Group 2). The use of local agents was more common in Group 2 (58% of patients) than in Group 1 (28% of patients). When no local agents were used, the risk of PTH was similar in both groups (Group 1: 3.6%, Group 2: 4.4%). Whether the association is due to lidocaine with epinephrine, the skills of surgeons, or both cannot be convincingly concluded from this retrospective study material.

In the literature, peritonsillar infiltration of lidocaine with epinephrine has been suspected to increase the risk of PTH due to masking of inadequate hemostasis, but the effect is expected to appear immediately as the vasoconstrictive effect of epinephrine wears off.¹⁴⁵ On the other hand, from a surgical point of view, without local anesthesia associated vasoconstriction, good visibility is achieved of the veins and every bleeding vessel will be coagulated during surgery. The better hemostasis and wound healing could appear later, at the end of the first postoperative week during the peak incidence of PTH. The increased risk of postoperative hemorrhage due to the effect of local anesthesia has not been reported before to our knowledge. In tonsillectomy studies on local anesthetics, the follow-up times are typically 24 hours or less and therefore secondary PTH cannot be detected. Local anesthetics inhibit wound healing by their antiproliferative effect on many cell types including mesenchymal stem cells essential in wound healing in a dose-dependent manner (in vitro and animal models); however, the clinical meaningfulness of this is not yet clear.¹⁴⁶ Also, epinephrine has been shown to decrease cell migration and potentiate persistent inflammation in infected wounds.¹⁴⁷ An open wound in the oral cavity is vulnerable, and even minor adverse effects of medications such as impairing wound healing may increase the risk of PTH. In our clinic, the use of local lidocaine with epinephrine in tonsillectomies has decreased over the years; however, it is used often in tonsillotomies, which are now more common than tonsillectomies in pediatric patients. Whether lidocaine with epinephrine increases the risk of PTH in tonsillotomies remains to be studied.

NSAIDs and dexamethasone were used for the majority of patients in large retrospective Studies I and II, and fortunately the risk of PTH or other complications was not increased. The evidence regarding the association of PTH with NSAIDs, and to a lesser extent also dexamethasone, is controversial probably due to many confounding factors. In our institution, the operation technique is quite homogenous, and the sample size was large, and thus the result is reassuring for the safe use of both NSAIDs and dexamethasone at least in our institution with the present perioperative treatment protocol. The systematic review (Study III) did not reveal an increased risk of PTH either. Guidelines recommend the use of NSAIDs and dexamethasone for the prevention of pain and PONV, and the evidence from our studies supports this conclusion.

6.3. POST-TONSILLECTOMY PAIN

Only a very few studies on tonsillectomy (pain or PTH) have been published that have a follow-up of more than few days. A study on adults (1995) with a follow-up of 10 days reported moderate to severe pain intensity lasting for 6 postoperative days.⁵³ In the study of Sarny (2012), 50% of patients experienced severe pain until the 6-7th postoperative day, then declining (pain type II, Figure 1).⁵⁴ In Study III (systematic review) and IV (ropivacaine study) the mean pain intensities were moderate to severe after tonsillectomy for 1–2 weeks and then declining, confirming results from few previous studies.

6.4. ANALGESIA

Systematic review revealed that the evidence on efficacy of analgesics for post-tonsillectomy pain is minimal due to lack of good/high quality studies. Follow-up periods should be longer (1-2 weeks) and pain should be measured separately at rest and on swallowing and preferably by global pain measurements, such as brief pain inventory (BPI).

Study III confirmed a weak to moderate analgesic effect of paracetamol, NSAIDs, dexamethasone, gabapentinoids, and dextromethorphan for post-tonsillectomy pain on the day of operation and dexamethasone in multiple doses beyond the first postoperative day. In the one included study on 40 adult patients, ketamine i.v. bolus of 0.5 mg kg⁻¹ after induction and infusion of 0.1 mg kg⁻¹ h⁻¹ until end of the surgery did not reduce pain intensity or need for opioids significantly during 24 hours of follow-up.¹⁴³ A difference may have been observed with larger patient material and longer follow up, given that ketamine has been shown to reduce postoperative pain in pediatric tonsillectomy patients.⁹⁷ Systematic review and meta-analysis in

pediatric tonsillectomy patients (2014) reported reduced pain intensities within first 4 hours and need for analgesics within 24 hours postoperatively in ketamine groups compared with control groups.⁹⁵ In the subgroup analysis, peritonsillar infiltration of ketamine was more effective than intravenous ketamine in reducing postoperative pain within 4 hours of follow-up (immediately after surgery -2.9 in ketamine groups compared to -0.8 in control groups, measured with pain intensity scale 0-10). Locally administered ketamine was suspected to be more efficient due to its direct effect on the peripheral nerve endings and longer lasting pharmacokinetic effect.^{97,149}

On the day of operation, pain is not yet severe, and is easily controlled at the hospital. On following days as pain intensity is moderate to strong, and it was obvious from studies III and IV that treatment with any analgesics or dexamethasone alone is not effective enough to reach clinically meaningful reduction (pain intensity less than 3/10).

In Study IV, ropivacaine did not reduce the peak pain intensity values or consumption of rescue medication during the 2h PACU follow-up, which is an indication of insufficient entry of drug to the effect site. Explanation could be fast clearance from the tissue, or that only small part of ropivacaine was in its non-ionized lipid soluble form (because of the acidic environment under the wound) and was therefore unable to pass nerve membrane sufficiently. Although ropivacaine failed to reduce pain intensity during the 2-week follow-up, consumption of paracetamol-codeine tablets was significantly reduced on the second week ($p = 0.006$). This was a secondary outcome; however, the large patient sample increases the probability, that the ability of topical ropivacaine to decrease pain intensity during the second postoperative week is a true (analgesic) effect. The reason why ropivacaine seemed to modify pain as late as on the second postoperative week could be partial prevention of hyperalgesia that declined sooner in the treatment group. A similar finding was reported in a tonsillectomy study comparing hot and cold technique in which the other side (tonsil) was operated with cold instruments and the other with a hot technique: pharyngeal pain intensity and otalgia were lower on the hot technique side compared to cold technique side on the day of operation, but higher on the second postoperative week.¹¹⁵ Authors suspected that slower healing on the side of hot technique resulted in more intense nociceptive stimuli on exposed nerve endings causing central sensitization, hyperalgesia and prolonged pain, and therefore the difference between sides appeared later, during the second postoperative week. The efficacy of topical ropivacaine for the prevention of post-tonsillectomy pain has been reported previously in pediatric patients and in mixed populations.²⁷ Surgery requires less invasive technique and need for coagulation in pediatric patients operated mainly for tonsillar hypertrophy, and thus the operation site (tonsillar bed) may be more permeable than in adults operated mainly for chronic tonsillitis, allowing topical anesthetics to pass to the effect site more easily.

7. LIMITATIONS

The weakness of Studies I and II is that because several simultaneous factors play a role in the pathogenesis of PTH that are not possible to detect in retrospective studies, causal conclusions cannot be made. Additionally, only limited insight is possible to problems rising at home after surgery.

Optimally, a systematic review and meta-analysis combines data from many high-quality studies resulting in a large patient population, giving the possibility to estimate treatment effects more precisely than is possible in single studies. In Study III, a thorough search was performed by using multiple databases and by hand searching reference lists of included trials, and therefore all relevant studies are likely to be included during the study period. Only good to high quality studies (Oxford Quality Scoring Scale was used for assessing quality) were included for the analysis and the overall risk of bias, measured by the Cochrane tool of bias, was low.¹¹¹ However, 12/29 studies did not report the primary outcome, and it is unclear how sample size was calculated, and how reliable obtained results within studies are. The overall risk of bias can be assumed higher, than shown by the Cochrane risk of bias tool, which maybe does not weigh the missing of the primary outcome in the calculation as much as it should. Combining results in a pooled meta-analysis was possible only in selected studies due to limited and heterogenic data. The meta-analysis was nevertheless conducted, with the description of this limitation, to allow rough comparison between studies and study groups. Due to these limitations, results of the systematic review must be interpreted with caution.

In Study IV, the use of paracetamol-codeine combination analgesics up to 8 times daily at home may have masked the effect of topical ropivacaine so that differences in pain intensities did not become significant. Due to intensive post-tonsillectomy pain, the standard use of analgesics was nevertheless considered only possible option for ethical reasons. The other issue that may have affected the outcome was that ropivacaine was applied in the squeezed swabs, so the dose was not exact and maybe was not high enough. Time of five minutes allowed for absorption had been used in similar studies, but it may have been too short; it was chosen for practical reasons, so that the application time would be within acceptable limits in everyday clinical practice.

8. FUTURE ASPECTS

Multimodal analgesia for tonsillectomy needs further developing. Antihyperalgesic adjuvants such as ketamine as intravenous infusion or locally for the prevention of post-tonsillectomy pain should be studied in adults. For safety reasons, it would be important to investigate whether lidocaine with epinephrine increases the risk of PTH in tonsillotomies. Well-conducted studies in post-tonsillectomy pain with follow up of 1-2 weeks are needed for improvement of care and patient satisfaction.

9. CONCLUSIONS

1. During the study period of 12 months, in our institution PTH was the most common complication, in adults 14.5% (primary PTH 1.3%, secondary PTH 13.2%, reoperation 1.5%) and in pediatric patients 7.1% (primary PTH 0.6%, secondary PTH 6.5%, reoperation 4.2%). In pediatric patients the overall incidence of unplanned postoperative contact was 14%, (revisits 10%, readmission 8%, pain 3%, fever 2.3%, PONV 1%).
2. Paracetamol, NSAIDs, dexamethasone, oxycodone, or 5-HT₃ antagonists were not associated with an increased risk of postoperative complications. The use of local anesthesia with peritonsillar infiltration of lidocaine with epinephrine was associated with an increased risk of secondary PTH among pediatric patients.
3. Tonsillectomy is a painful procedure. The mean pain intensity was moderate to severe for 1–2 weeks postoperatively in adult patients, despite analgesic treatment.
4. Systematic review revealed that the evidence on efficacy of analgesics for post-tonsillectomy pain is minimal due to lack of good quality studies. Paracetamol, NSAIDs, dexamethasone, gabapentinoids, and dextromethorphan had a weak to moderate analgesic effect on post-tonsillectomy pain on the day of operation. Dexamethasone in multiple doses had analgesic efficacy beyond one postoperative day; however, risks should be considered if treatment is prolonged. None of the studied analgesics or dexamethasone alone were effective enough to provide clinically meaningful analgesia (pain intensity less than 3/10) for treatment of post-tonsillectomy pain, and therefore multimodal analgesia is needed in order to offer patients adequate pain control.
5. Topical ropivacaine applied to the tonsillar bed after removal of the tonsils failed to reduce post-tonsillectomy pain during the first postoperative week but seemed to modify pain during the second postoperative week.

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APPENDIX 1

TOPICAL ANESTHESIA IN THE TREATMENT OF POSTOPERATIVE PAIN IN ADULT TONSILLECTOMY PATIENTS 1–14 DAYS AFTER SURGERY

Dear patient, we appreciate your participation in this study. Please answer all of the following questions.

A. Background information

Surname:

Year of birth:

B. Pain during the past 24 hours

Choose the most appropriate alternative using the 0–10 pain scale, 0 = no pain, and 10 = unbearable pain

0 1 2 3 4 5 6 7 8 9 10

1. Estimate the worst level of pain while at rest during the past 24 hours

<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
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2. Estimate the worst level of pain while swallowing during the past 24 hours

<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
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3. How many tablets of Panacod have you taken during the past 24 hours? (0–8)
4. How many tablets of Ibuprofen 600 mg have you taken during the past 24 hours? (0–3)
5. Has the pain woken you up at night during the past 24 hours? (No / Yes)

C. Complications

6. Have you felt nauseous during the past 24 hours? (No / Yes)
7. Have you vomited during the past 24 hours? (No / Yes)
8. Have you had trouble swallowing for reasons other than pain (such as numbness of the throat) during the past 24 hours? (No / A little; I am able to swallow solid food / Considerable trouble; I am only able to swallow liquids)
9. Have you had the sensation of a foreign object in your throat during the past 24 hours? (No / A little / A great deal)
10. Have you felt liquid trickling into your nose or windpipe while swallowing (“going down the wrong pipe”) during the past 24 hours? (No / A little / A great deal)
11. Have you experienced bleeding in the area affected by the surgery during the past 24 hours? (No / A little blood mixed with saliva / Yes, clear blood)

D. Feedback

12. What would you like to tell the medical staff or research group?

APPENDIX 2

POSTOPERATIVE PAIN MEDICATION FOR ADULT TONSILLECTOMY OUTPATIENT

Recommendation for physician at the Helsinki University Hospital, Department of Otorhinolaryngology—Head and Neck Surgery

Medication when the patient does not have contraindications:

- Ibuprofen 600–800mg 3 times daily, regularly for one week, then as needed. N = 100. Alternatively, another nonsteroidal anti-inflammatory drug (NSAID)
- Paracetamol 500 mg + codeine 30 mg (Panacod®) 1–2 tablets 2–4 times daily, regularly for one week, then as needed. N = 60–100. The prescription must be written with a statement that it may not be renewed.
- Sodium picosulfate (Laxoberon®) 2.5mg capsule prescription. Dosage 2–4 capsules in the evening as needed. N = 50.

Alternative medication when contraindications to NSAIDs:

- Paracetamol 1 g perorally 3–4 times daily, regularly for one week, then as needed. N = 100.
- Tramadol 50–100 mg perorally 1–3 times daily, regularly for one week, then as needed. N = 100.

If the above medication is inadequate and the patient comes to the hospital because of intolerable pain, consider replacing paracetamol + codeine or tramadol with long-acting oxycodone + naloxone (Targiniq®) 10/5 mg 1 tablet perorally two times daily, N = 14.

The first dose is administered at the hospital and patient is monitored 3–4 hours prior to discharge. The patient must be of normal size (> 50kg), without risk factors for misuse and understand instructions. Prescription must be written with a statement that it may not be renewed.

Contraindications for NSAIDs

- Hypersensitivity (10% of patients with asthma)
- Treatment with anticoagulants
- Kidney deficiency
- Gastric ulcer
- Cardiovascular disease (according to the degree of severity)
- (Relative contraindication for age > 70 years; high doses of NSAIDs can burden the kidneys)

Observe contraindications/caution with opioids!

- Hypersensitivity
- Sleep apnea (obstructive/central): Tramadol MAY be used in mild sleep apnea
- Tendency to biliary spasms: NO paracetamol/codeine
- Respiratory problems: Broncho pulmonary disease (depending on severity), neuromuscular disorders: NO opioids
- Hepatic impairment: NO with paracetamol/codeine, others according to the degree of severity
- Renal impairment: Opioids according to degree of severity
- CYP2D6 ultrafast metabolite (known or at-risk based on ethnicity): NO paracetamol/codeine or tramadol
 - o Codeine is metabolized rapidly to morphine and may accumulate, which is reflected in decreased alertness and respiratory depression
 - o The same risk with tramadol (part of the effect is through the opioid receptor)
 - o Prevalence % in different ethnic groups: East Africa (Ethiopia, Somalia) 29%, Middle East 20%, African American 3–7%, Asia 1–2%, Northern Europe 1–2%, Finnish 7%, Mediterranean countries 5–10%

APPENDIX 3

POSTOPERATIVE PAIN MEDICATION FOR PEDIATRIC TONSILLECTOMY PATIENT

Recommendation for physician at the Helsinki University Hospital, Department of Otorhinolaryngology—Head and Neck Surgery

Pain medication is determined individually, taking into account the procedure, the patient's underlying conditions, age and weight. Remember the recipe Sic! when the dose exceeds the instructions in Pharmaca Fennica.

Medication when the patient does not have contraindications (principles for the operation of tonsils):

- Adenotomy: paracetamol + ibuprofen / naproxen
- Tonsillotomy: paracetamol + ibuprofen / naproxen
- Tonsillectomy:
 - o paracetamol + ibuprofen / naproxen + tramadol if necessary (titration at hospital)
 - o OR ibuprofen / naproxen + paracetamol / codeine (> 12 yrs only and indication other than snoring / sleep apnea)

Paracetamol:

- The first 2 days 100 mg/kg/day divided into 3-4 doses (e.g. 25 mg/kg x 4), followed by 60 mg/kg/day divided into 3 doses (20 mg/kg x 3) perorally (max 3g/day)
- Paracetamol mixture 24 mg/ml or tablets 125 mg, 250 mg, 500 mg perorally.

NSAIDs:

- Naproxen mixture 25 mg/ml (5 mg/kg x 2) perorally.
- Ibuprofen 40 mg/kg/day divided in 3 doses perorally/per rectum, peroral max. dose 2400 mg/day.

Weak Opioids:

- Codeine:
 - o In CYP2D6 ultra-fast metabolizers, codeine is metabolized rapidly to morphine and may accumulate, which is reflected in decreased alertness and respiratory depression. The same risk is with tramadol (part of the effect is via the opioid receptor) (ethnic at-risk groups, see recommendation for adults).
 - o In patients over 12 years of age who have undergone tonsillectomy/adenotonsillectomy for indications other than snoring/sleep apnea, at discretion: paracetamol 500 mg/codeine 30 mg (single dose of codeine 0.5-1 mg/kg).
- Tramadol:
 - o If pain after tonsillectomy is severe in patients younger than 12 years of age, tramadol may be titrated at hospital to determine the appropriate minimal effective dose (usually a maximum of 1 mg/kg 1–3 times daily as needed). Follow-up must be at least 3-4 hours.
 - o Patients older than 12 years of age operated for tonsillectomy/adenotonsillectomy for other than snoring/ sleep apnea: Tramal 50 mg capsules 1-2 x 3-4/day (single dose 1-2 mg/kg).

